THE YEAR BOOK *of*

ENDOCRINOLOGY

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EDITED BY

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INTRODUCTION

Since the first YEAR BOOK devoted entirely to endocrinol ogy appeared in 19 0 many striking changes have occurred Refined technics have made it possible to measure accurately microgram amounts of then unknown substances Single hormones have developed into families of molecules witness the thyronines and tyrosines the ACTH MSH (melanocyte stimulating hormone) adrenal growth factor complex and the adrenal steroids It may be salutary to remind ourselves that 10 years ago there was room for controversy as to whether the actions of the adrenal cortex could be explained by a single steroid The burgeoning sciences of genetics and immunology are also strongly influencing endocrinology Many endocrine disorders are familial e g goitrous hypo thyroidism some of the di orders of sex differentiation pheochromocytoma congenital virilizing adrenocortical hy perplasia hyperparathyroidism and endocrine adenomatosis to mention just a few The recognition of autoimmune anti bodies in the blood of patients with chronic thyroiditis and myxedema has stimulated both immunology and thyroidol ogy Parallel discoveries are undoubtedly just around the corner for the other glands Immune mechanisms have been used successfully to measure microamounts of pituitary hor mone in blood and while technically not free from pitfalls may be expected to have similar usefulness for measurement of other hormones Preliminary data for insulin are already available Just beginning to make sense are the enzymatic action of steroid hormones In years gone by many of us mixed up steroids and enzyme systems and reported crude effect including an action of estrogen on dehydrogenases but the amounts used and the crudeness of the methods per mitted no extension of these observations to the living ani mal The fine technics of Claude Villee were the first to clarify mechanisms by which estrogens might provide energy through their action on isocitric dehydrogenase to explain their well known actions in vivo These studies were further extended by Talalay whose work suggested that estrogens might in fact act as coenzymes in a hydrogen transfer sys

tem though more recently Villee whose report is abstracted in the chapter on The Reproductive System has actually separated the estrogen sensitive soluble pyridine nucleotide transhydrogenase from the estradiol dehydrogenases in human placenta It is apparent that we are much further along in understanding the actions of steroids than we were in 1950 A second example of a steroid dependent enzyme system has been demonstrated by Lewis Engel He reported (Conference on the Biologic Effects of Steroids Vergennes Vt Sept 27 Oct 2 1959) that corticosterone and hydrocortisone *in amounts so small as to approach those occurring* naturally in the presence of diphosphopyridine nucleotide stimulates glutamic dehydrogenase Testosterone by itself is ineffective in this system but when added to corticosterone blocks the stimulating action It is tempting to speculate that this may be the first demonstration of an enzymatic mechanism that would explain the anabolic effect of testosterone The system is apparently specific for active corticosteroids since the inert isomers are ineffective The enzymology of thyroid hormone synthesis has also been clarified still lacking is the enzyme which performs the important function of coupling the two tyrosine rings to produce thyroxin The enzyme defects in thyroid hormone synthesis like the enzyme defects of adrenocortical steroid synthesis are found to have genetic implications since they are familial

Pinpointing of exact mechanisms is not limited to enzymology genetics and immunology The neuroanatomists and neurophysiologists have localized to millimeter areas the hypothalamic sites controlling the several pituitary hormone secretions This is a long step toward demonstrating the mechanisms that coordinate the actions of the body s two great integrators—the nervous and endocrine systems But the hypothalamus has no monopoly on endocrine control The brilliant work of Gordon Farrell has localized to the pineal gland the elaboration of a lipid soluble neurohumor that directly controls the release of aldosterone from the adrenal cortex

It is no longer presumptuous to ask whether neoplasia of endocrine sensitive organs may result from prolonged stimulus to these organs The combination of chromophobe adenoma of the pituitary and hypogonadism was ascribed in the

past to crowding out of gonadotrophin by the adenoma Now the question is being asked Can the pituitary respond by the formation of an adenoma to long standing gonadal de ficiency Furth has produced adenomas of the pituitary in mice by radioiodine induced hypothyroidism These tumors elaborate large amounts of thyrotrophin which incidentally appears to be free of exophthalmos producing factor Evi dence is lacking that chromophobe adenomas in hypogon adal people elaborate gonadotrophin A similar situation is found however in parathyroid adenomas which have been found rarely in patients with long standing steatorrhea Since steatorrhea can produce secondary hyperplasia of the parathyroid considerable controversy has resulted from the suggestion that parathyroid adenomas in patients with stea torrhea may be more than coincidental

The exact amino acid sequences have been worked out for a number of protein and peptide hormones The beautiful work of Sanger was appropriately recognized by the award of the Nobel Prize (his lecture delivered December 10 1958 is ab tracted in the chapter on Carbohydrate Metabolism) ACTH melanocyte stimulating hormone and the posterior pituitary hormones have also been characterized Chemical modification of thyroxin has led to a number of thyroid ana logs with divergent actions In some the action on the heart is increased e g triiodothyronine triac and tetrac while in others it is minimized e g triprop and dextrothyroxin Minimization of myocardial action has led to the interesting observation that by giving thyroxin analogs one can lower the serum cholesterol level without accelerating the heart rate Similarly androsterone which has always been con sidered a weak metabolite of testosterone and from the re cent brilliant work of Seymour Lieberman also of dehydro epiandrosterone can in suitable circumstances lower the serum cholesterol level

For 15 years it has been known that the synthetic goitro gens stimulate hyperplasia of the thyroid gland In suitable strains of rodents these agents can induce not only hyper plasia but tumors which infiltrate metastasize and can be transplanted Some of the goitrogenic compounds are given for other purposes e g sulfonamides for infection One aminotriazole is used as a weed killer The Great Cranberry

Scare of 1959 resulted from the detection of aminotriazole in the berries That it was found at all is a tribute to modern methods for the chemical detection of minute amounts of materials Public Law 85 929 September 26 1958 (85th Congress H R 13254) intended to prevent adulteration of foods prohibits the release of foods containing additives that are found to induce cancer when ingested by man or animal Certainly none of us wishes carcinogens in our food Goitrogens however are compounds that when given in extremely large amounts for extremely long times to specifically susceptible strains of rodents produce cancers of the thyroid but according to adequate actuarial information do not do so in man Furthermore the amounts that could reasonably be ingested in cranberries are obviously insignificant Greater amounts of naturally occurring goitrogens are ingested by people who eat turnips or soybeans (see Thyroid Gland) A similar situation is found in the use of stilbestrol to caponize cockerel or to fatten cattle Again detection of minute amounts of estrogen in the meat of caponettes or stilbestrol treated beef is a tribute to modern chemical technics Estrogens also occur naturally in foods and in this case published information suffices to show that stilbestrol is *not* a carcinogen in man In fact the series published by Henneman and Wallach (J A M A 171 1637 1642 Nov 21 1959) and of Mustacchi and Gordan (A Segaloff [ed] *Breast Cancer* [St Louis C V Mosby Company 1958] pp 163 169) suggest that in human subjects stilbestrol may *prevent* cancer! Meanwhile how many hundreds of thousands of women properly taking stilbestrol for good medical reasons have been scared out of their wits by headlines? Careful screening of insecticides by workers at the Food and Drug Administration has shown that the insecticide DDD causes atrophy of the adrenal cortex The *o p* derivative has been found to be the most effective and least toxic and the late Delbert Bergenstal of the National Cancer Institute found that it caused regressions of widespread adrenal cancer

The studies of Daughaday and of Slaunwhite and Sandberg have clarified the important matter of the binding of cortisol (hydrocortisone) to serum proteins and its transport in the blood The cortisol binding protein to which it adheres six thousand times more strongly than to albumin has been

named transcortin Kenneth Savard the expert steroid chemist at the University of Miami has suggested that a protein carrying cortisol might be called cor tote and if it binds so tightly cor set Cortisol binding is increased in pregnancy and after administration of estrogens and certain derivatives of 19 nortestosterone High levels in the plasma therefore probably do not indicate increased adrenocortical function but rather increased binding protein just as in the case of thyroid hormone binding and transport

Perhaps the most important development in our knowledge of adrenocortical disease in the past few years is the tardy recognition that Cushing s disease (bilateral adrenocortical hyperfunction) is often associated with pituitary tumors These have been recognized most commonly in patients whose Cushing s disease has been treated by bilateral adrenalectomy Practically this rediscovery leads us to wonder whether adrenalectomy is really the best treatment for Cushing s disease not only because the pituitary tumors are apparently stimulated to grow by this operation but also because adrenalectomy produces Addi on s disease and a lifetime demand for exogenous corticosteroids Theoretically this ob ervation is a major confirmation of the pituitary origin of Cushing s di ease and brings us full cycle to Harvey Cushing s interpretation in 1932 Except in rare cases in which the disease is o fulminating that the surgeon s hand is forced it would appear that the therapy of Cushing s disease should be directed to the pituitary rather than the adrenal This has long been my personal preference (Gordan and Lisser *Endocrinology in Clinical Practice* [Chicago Year Book Publishers Inc 1953] p 158) A recent personal communication from Louis Soffer reports satisfactory control of Cushing s disease by pituitary irradiation unilateral adrenalectomy or a combination of both measures in 75% of his patients A reservation in this matter is the diagnostic problem of ascertaining that the disease is due to bilateral adrenocortical hyperplasia and not to tumor though I personally believe that this can usually be done by adequate clinical chemical and roentgen studies Another reservation is based on the demonstration by Swedish workers that transplantation of adrenal tissue in the thigh muscles at the time of bilateral adrenalectomy supplies adequate adrenal function

Also from Sweden is the demonstration of one of the major disadvantages of induced Addison s disease In the 1957 1958 epidemic of Asian influenza 5 of the 10 deaths in the city of Malmo occurred in patients with adrenal insufficiency

Murray Barr s epoch making discovery of the chromatin blob on the nuclear border of cells from females first applied to the elucidation of disorders of sex differentiation by Polani and his co workers in 1954 is now used routinely Until technics become simplified it is not likely to be supplanted by the more elegant and definitive chromosome counts stemming from the beautiful work of C E Ford Chromosome counts have important clinical implications since it now appears that the chromosomal pattern in chromatin negative gonadal dysgenesis is XO rather than XY and in chromatin positive Klinefelter s syndrome is XXY rather than XX Mongolism is also associated with an abnormal chromosome which is not one of the sex chromosomes

Finally the careful clinical screening of androgen derivatives by the Cooperative Breast Group of the Cancer Chemotherapy National Service Center headed by Albert Segaloff has led to important preliminary data Blackburn and Childs have presented carefully derived and conservatively interpreted data suggesting that 2 alpha methyldihydrotestosterone a weak androgen may be equal to or better than testosterone propionate in the treatment of advanced breast cancer Segaloff has found that delta 1 testololactone produces regressions similar in number to those obtained by testosterone propionate What is particularly significant here is that delta 1 testololactone has no apparent endocrine activity It is not androgenic it does not inhibit gonadotrophin output The other promising compound 2 alpha methyl dihydrotestosterone does not inhibit gonadotrophin secretion either Thus the efficacy of androgen derivatives in the treatment of advanced breast cancer appears to be separable from their androgenicity and their ability to inhibit gonadotrophin secretion These are therefore simply chemotherapeutic agents which suppress cancer by unknown means The concept of hormone dependency of human breast cancer has been dealt a serious blow by these observations

As in the past I take pleasure in thanking the Year Book Publishers for a relationship which has been thoroughly

comfortable and rewarding to me To them goes the credit for culling the great mass of medical journals and seeing that articles of endocrine significance reach me To them also goes the credit for the superb job of publication to which we have become accustomed I wish also to acknowledge my indebtedness to Miss Frances Wetherhold and Miss Dawnna Renfro for expert editorial and secretarial aid and to Drs I S Edelman Wallace V Epstein and Francis Greenspan for critical review of parts of the manuscript

GILBERT S GORDAN

► While the exact nature of the hypothalamic neurohumors involved in pituitary secretion has not been established it appears that neurohypophysial hormones may have similar effect Since the neurohypophysis is anatomically an outpouching of the hypothalamus this similarity is not surprising As will be seen in the chapter The Adrenal Cortex the neurohumor serotonin has a stimulatory action on that organ which incidentally is also directly responsive to neurohypophysial hormone Another neuroendocrine tissue the adrenal medulla like the hypothalamus and posterior pituitary gland is responsive to reserpine (see the chapter The Adrenal Medulla) —Ed

Further Study of an ACTH Releasing Protein from Hypophysial Portal Vessel Plasma is presented by John C Porter and H W Rumsfeld Jr[1] (Southwestern Med School) Blood that accumulated in the sella area of dogs after removal of the pituitary was aspirated The source of the blood was in part from the hypophysial portal vessels The plasma was fractionated by the method of Cohn and hydrocortisone treated intact rats were used to estimate ACTH releasing activity

The ACTH releasing activity of portal vessel plasma is found in the protein fraction III_0 This fraction contains three major proteins with isoelectric points of pH 4 4 5 1 and 6 6 Starch column electrophoresis showed that intermediate peak 2 or a component of this peak was associated with the active substance Moving boundary electrophoresis demonstrated a single component with a stipulated mobility midway between peaks 2 and 3

The activity of fraction III_0 was destroyed by incubation with trypsin and pepsin and by reflux with 0 1N NaOH but was stable to reflux in 0 1N HCl After dialysis against distilled water for 24 hours ACTH releasing activity was present in the dialysate

The study indicates that the constituent in portal plasma responsible for ACTH release in the corticoid treated rat can be dissociated from plasma proteins The protein component described may carry a neurohumoral agent which increases rate of release of ACTH

Neurohypophysial Hormones and Release of Gonadotrophins Experiments have indicated that the hypothalamus

(1) F dx 1xy 64 948 9 4 J 1959

regulates secretion of gonadotrophic hormones by the anterior pituitary Recently experiments have shown that posterior lobe extracts can induce release of corticotrophin in normal animals and in hypophysectomized animals with a functioning pituitary graft in the anterior chamber of the eye and in animals with hypothalamic lesions Commercial antidiuretic preparations induce significant increase in thyroidal uptake of radioiodine in normal rats but not in hypophysectomized rats Extracts containing the antidiuretic activity of the posterior lobe induce widening of the epiphysial cartilage in normal young rats probably via release of growth hormone Natural or synthetic oxytocic hormone may stimulate the release of lactogenic hormone

L Martini I Mira A Pecile and S Saito (Univ of Milan) investigated the excretion of urinary gonadotrophin in rabbits before and after administration of different posterior pituitary preparations Mean urinary gonadotrophin output was 0 065 μg estrone equivalent per day per rabbit without significant spontaneous day to day or seasonal variations After intravenous Pitressin or purified lysine vasopressin in large amounts urinary gonadotrophins increased significantly beginning immediately after teatment and lasting some days After Pitocin and synthetic oxytocin were given a sharp increase occurred in urinary gonadotrophins on the next day which returned to normal on the 2d day Neither Pitressin lysine vasopressin nor Pitocin produced any modification of the uterine weight when injected subcutaneously into immature female mice indicating they were not contaminated by pituitary gonadotrophins

In nonpregnant women urinary gonadotrophins may reflect the secretory rate of these hormones by the anterior pituitary gland Posterior pituitary hormones may accelerate release of gonadotrophins from the anterior pituitary Some known or unknown peptide in the neurohypophysis and present in the preparations used may be the neurohumoral substances involved in the physiologic regulation of gonadotrophin secretion

Studies on Mechanism of Hypothalamic Control of Thyrotrophin Secretion Effect of Intrahypothalamic Thyroxin Injection on Thyroid Hypertrophy Induced by Propylthiouracil in Rat Recent studies have suggested that thyroid

hormones can inhibit thyrotrophin secretion only through a direct effect on the anterior pituitary and that the hypothalamus is not responsive to altered thyroid hormone levels However hypothalamic lesions can significantly depress thyroid activity Takashi Yamada[3] (Univ of Oregon) injected 0 25 µg thyroxin into the anterior hypothalamus of rats that were chronically treated with propylthiouracil

In control rats that received propylthiouracil and had injections of saline into the hypothalamus, thyroid hypertrophy resulted In contrast goitrogenesis was completely prevented in 7 of 8 rats that received thyroxin in the anterior hypothalamus Adrenal weight increased in all treated animals Systemic injection of the same amount of thyroxin did not inhibit goiter formation

Histologic examination of the hypothalamus in both thyroxin and saline treated rats showed that the tips of the needles had been situated in the thyrotrophin area which lies in the midline between the paraventricular nucleus and the median eminence The capillary tufts of the hypophysial portal system in the median eminence were markedly dilated in rats in which thyroid hypertrophy occurred Such changes were absent or minimal in rats without thyroid hypertrophy

The present experiments did not indicate whether the inhibitory effect of intrahypothalamic thyroxin injections was produced by direct action on neural elements in the hypothalamus or by diffusion of the injected thyroxin through the hypophysial portal vessels to the anterior pituitary Other studies have shown that equivalent doses of thyroxin injected into either the hypothalamus or the pituitary will inhibit thyroid gland hypertrophy Also radiothyroxin diffuses rapidly from the site of injection in the hypothalamus but is not significantly concentrated in the pituitary These facts suggest that receptors in both the hypothalamus and anterior pituitary exist which respond to alteration in the level of circulating thyroxin

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ADENOHYPOPHYSIS

► Two lines of endeavor are adding greatly to our knowledge of adenohypophysial function. One is the preparation of pituitary hormones from

various species in remarkably pure form and the production of specific antibodies to them Another is the physiologic study of patients with advanced cancer or severe diabetes who have been subjected to hypophysectomy or pituitary stalk section in an attempt to alleviate these serious disorders An interesting observation in hypophysectomized patients is that some maintain thyroid function or even develop hyperthyroidism apparently because of autonomous thyroid adenomas (see the chapter Thyroid Gland) Another is the demonstration that aldosterone secretion may continue or even be augmented after hypophysectomy By way of contrast suprasellar tumors result in inability to increase aldosterone secretion after salt restriction (Hokfelt and Luft Acta endocrinol 32 177 1959) Unusual causes of hypopituitarism including tapeworm infestation and sarcoidosis have been described That human growth hormone is effective in man has now been established The hypercalciuric effect originally noted by Ikkos and Luft (Lancet 1 720 Apr 5 1958) now appears to result only from overdosage Since administration of large amounts of growth hormone can result in increased urinary calcium loss in persons without breast cancer it is clear that increased calcium excretion cannot be taken as evidence that growth hormone accelerates this neoplastic growth.

Of great interest, but too recently published for inclusion in this volume are a number of clinical applications of immunologic assays for pituitary hormones At the 1959 Laurentian Hormone Conference Charles H Read of the University of Iowa described an apparently specific assay for growth hormone based on inhibition of a system using growth hormone-coated erythrocytes against an antiserum to human growth hormone Antiserum was prepared by subcutaneous administration of the Raben human growth hormone preparation to adult female rabbits The antiserum so prepared inhibits growth hormone activity on the tibial epiphysis of the rat and agglutinates tanned sheep red cells coated with growth hormone Read found no reaction except with the human preparation monkey growth hormone and as might be expected from the previous studies of Wilhelmi fish growth hormone Using inhibition of complete hemagglutination as a quantal response he found that the serum of normal children contains 90 600 mμg /ml of growth hormone that of adults 90 400 while in acromegaly the value ranged from 500 to 1,200 In 9 hypopituitary patients less than 90 mμg /ml was found Administration of 4 mg of the Raben growth hormone preparation to 3 hypopituitary patients raised the blood level to 300 mμg /ml. Fishman McGarry and Beck (Proc Soc. Exper Biol & Med 102 446 1959) confirmed the findings of Hayashida and Li that growth hormone antiserums do not cross react with growth hormone preparations from other species These technics will obviously have wide spread value in the measurement of protein and peptide hormones —Ed.

Section of Pituitary Stalk in Monkeys Division of the pituitary stalk is regularly associated with derangement of functions that are dependent on the neurohypophysis but not in those that depend on the pars distalis Ferrets can apparently continue normal estrus function after division of the pituitary stalk and without re establishing vascular connections

R L Holmes E Brodie Hughes and S Zuckerman[4] (Univ of Birmingham) cut the pituitary stalk in female monkeys and separated the cut ends by using a polythene

(4) J F doc 1 18 305 318 May 1959

pituitary trophic hormones which regulate the functions of the thyroid adrenals and gonads

In 7 patients skull x rays showed expansion of the sella turcica by a tumor The commonest symptoms were head aches nausea and vomiting followed in months or years by failing vision Symptoms began between ages 4 and 12 In the other 19 patients the cause of the pituitary insufficiency was unknown Growth was retarded earlier usually between 1 and 4 years None had symptoms or signs of a tumor

All 7 patients with tumor showed besides deficiency of growth hormone depressed function of target organs due to

INCIDENCE OF POSITIVE LABORATORY FINDINGS

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deficiency of pituitary trophic hormones Six had lowered thyroid function and 2 increased insulin sensitivity and hy poglycemic unresponsiveness Of 2 tested 1 showed a de crease in water diuresis after a water load Abnormally low urinary 17 ketosteroid excretion was found in 2 patients in whom it was measured In 14 of the 19 patients without tu mor failure of production of one or more of the trophic hor mones was inferred because of the low level of function of the respective target organs

The laboratory findings often corroborated the diagnosis of pituitary infantilism (table) 17 ketosteroid and follicle stimulating hormone excretion giving the best correlation Neither test is of diagnostic value until puberty and neither can be used to establish the diagnosis during childhood The test most easily carried out and of greatest diagnostic value in childhood is water load excretion This test reflects closely the functional integrity of the pituitary adrenocorti cal mechanism In 75% of the patients either thyroid or adre

nocortical hypofunction was demonstrable therefore in a significant proportion of cases diagnosis can probably be established before puberty

Six patients were given various growth fractions over a number of year without significant effect The 13 who had hypothyroidism received thyroid but without any marked change in the clinical condition The 4 with low excretion of urinary 17 hydroxycorticosteroids and abnormal water load excretion were given thyroid and cortisone Water excretion improved but otherwise there was no benefit Two were subjectively improved Three were given chorionic gonadotrophin which led to some testicular maturation and a rise in urinary 17 ketosteroid excretion and virilization but these regressed when treatment was stopped

Most boys were given testosterone Growth spurted weight was gained the frame broadened markedly and muscles developed The voice became lower and secondary sexual characteristics appeared As much as 5 in was added in the first 6 months or 1 year In girls estrogens were given with androgens resulting in near normal growth of pubic hair and a spurt of growth without virilization

Treatment with sex hormones has a definite place in management of the child with hypopituitarism but not before the usual age of puberty In the absence of an effective growth hormone preparation treatment of choice is substitution therapy with testosterone and estrogen since these cause a growth spurt with concomitant weight gain and virilization or feminization

[Worthy of note is the well documented observation that in childhood and adolescence severe hypopituitarism is not necessarily associated with dwarfism In fact growth may be excessive as a result of the hypogonadotrophic eunuchoidism The late John Peters pointed out and it has been the observation of many others that the damaged pituitary first loses its ability to elaborate gonadotrophin and only in very severe or advanced lesions is growth hormone activity lost —Ed]

Association of Pituitary Hypofunction with Chronic Diarrhea Report of Two Cases in which severe malnutrition with chronic diarrhea was followed by evidence of permanent pituitary damage is presented by G A Elliott T H Bothwell A Sandler D Rabinowitz and S Siew[6] (Johannesburg Gen l Hosp) In both cases though especially in the

first this hypofunction seemed to be due to organic rather than functional changes in the gland

CASE 1—Man 54 had unequivocal signs of irreversible panhypopituitarism which developed after a period of prolonged and severe diarrhea Despite remission of the diarrhea the patient s general condition did not improve and he had weakness impotence intolerance to cold loss of secondary sex hair and mild refractory anemia Biochemical tests made several years after onset of the condition confirmed the presence of pituitary hypofunction and there was a dramatic response to end organ replacement therapy

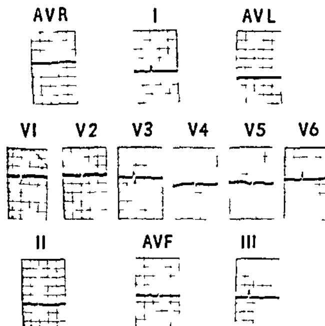
CASE 2—Woman 46 had chronic pancreatitis with diabetes steatorrhea and protein deficiency for several years Clinically she showed the features of pituitary insufficiency extreme intolerance to cold hoarseness loss of secondary sex hair and anemia Besides the diabetes showed a striking amelioration in the last few weeks of life Glycosuria disappeared and the sugar tolerance curve returned toward normal At this stage she became so sensitive to the effects of in ulin that it was discontinued and serial laboratory studies demonstrated an appreciable fall in serum protein bound iodine and in urinary excretion of follicle stimulating hormone and 17 ketosteroids At autopsy 30% of the anterior pituitary showed necrosis

The pituitary necrosis in Case 2 may have been secondary to the chronic malnutrition However it may have been related to the diabetes In effect Case 2 represented an example of the Houssay phenomenon in man

► [These patients are unusual in that the damage to the pituitary appeared to be permanent I have seen only 1 such case although transient hypopituitarism manifested by retardation in growth and sexual development in children or loss of gonadotrophic function in adults is common —Ed]

Electrocardiographic Changes in Hypopituitarism of Pregnancy W F Bernart and A M deAndino Jr (Univ of Puerto Rico) observed that 19 of 22 patients with well documented hypopituitarism of pregnancy showed definite ECG changes Seventeen with 12 lead tracings were abnormal Small flattened or inverted T waves were generally seen plus small P waves in most leads Low voltage of QRS complexes was uncommon Left axis deviation was rare Prolongation of the Q T interval and 1st degree heart block also were unusual though the mean P R interval was slightly prolonged Oral administration of thyroid in small doses did not significantly alter the ECG A fairly typical ECG is shown in Figure 4 This patient had had a postpartum hemorrhage from retained placental parts at age 34 The tracing was taken at age 40 before the start of replacement therapy

(7) Am H rt J 5 31 238 F b y 1958



F 4—Cha ges FCC hypop t t m f p gn n y (Co rt f B t W F a d d A d V M J V H rt J 55 231 38 F br y 1958)

Because depression of the functions of the anterior pituitary is not uniform after postpartum necrosis there are variations in the target organ response The ECG seems to reflect these changes However they do not appear to be diagnostic of any particular hormone deficiency and some of these abnormalities are seen with varying frequency in Addison s disease and primary myxedema

Hypophysectomy during Pregnancy in Patient with Cancer of Breast Case Report with Hormone Studies is presented by B Little O W Smith A G Jessiman H A Selenkow W van t Hoff J M Eglin and F D Moore[8] (Boston)

Woman 37 25 weeks pregnant had clinical signs of metastatic breast carcinoma Hypophysectomy was performed Diabetes insipidus developed as expected She was discharged and medication consisted of 75 mg cortisone and 90 mg desiccated thyroid daily Pit

(8) J Cl E doc 1 18 4 5-443 M y 1958

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The pituitary necrosis in Case 2 may have been secondary to the chronic malnutrition However it may have been related to the diabetes In effect Case 2 represented an example of the Houssay phenomenon in man

► [These patients are unusual in that the damage to the pituitary appeared to be permanent I have seen only 1 such case although transient hypopituitarism manifested by retardation in growth and sexual development in children or lo s of gonadotrophic function in adult i common —Ed]

Electrocardiographic Changes in Hypopituitarism of Pregnancy W F Bernart and A M deAndino Jr[7] (Univ of Puerto Rico) observed that 19 of 22 patients with well documented hypopituitarism of pregnancy showed definite ECG changes Seventeen with 12 lead tracings were abnormal Small flattened or inverted T waves were generally seen plus small P waves in most leads Low voltage of QRS complexes was uncommon Left axis deviation was rare Prolongation of the Q T interval and 1st degree heart block also were unusual though the mean P R interval was slightly prolonged Oral administration of thyroid in small doses did not significantly alter the ECG A fairly typical ECG is shown in Figure 4 This patient had had a postpartum hemorrhage *from retained placental parts at age 34 The tracing* was taken at age 40 before the start of replacement therapy

(7) Am H a t J 55 231 38 F b u y 1958

There is abundant evidence that undernutrition produces hypopituitarism The converse that overnutrition produce hyperpituitarism would explain the observations made on obese children Increased growth earlier puberty and increased adrenocortical activity could be explained on the basis of this concept The change in 17 ketogenic steroid excretion described in these patients might be due to an alteration in pituitary activity resulting from the change from over to undernutrition/Thus hypothesis might reconcile the views of those who consider obesity in childhood to be entirely nutritional in origin and those who believe it to be an endocrine disorder

Pituitary Irradiation with High Energy Proton Beams Preliminary Report The rationale and technic of pituitary irradiation with high speed protons and the initial physiologic changes after proton irradiation are presented by C A Tobias J H Lawrence J L Born R K McCombs J L Roberts H O Anger B V A Low Beer and C B Huggins[1] (Univ of California) High energy beams when focused travel in a straight beam with little divergence and penetrate to a uniform and well defined range producing maximal ionization just before stopping Thus they are peculiarly suitable for pituitary irradiation A multiple plane rotational technic with 340 Mev proton beam from the 184 in synchrocyclotron was used Peak doses of 14 000 30 000 rad at the center of the pituitary were administered to 26 patients with metastatic breast cancer The patients had progressive disease and had exhausted other therapeutic possibilities before having pituitary irradiation Most were at the terminal stage at onset of radiation therapy

The most valuable criteria for assessing the changes in pituitary function after irradiation in these patients were radioiodine uptake and 24 hour urinary pituitary gonadotrophin excretion Of 18 patients 11 showed marked depression of iodine uptake In 8 of 16 patients a marked drop in gonadotrophin excretion occurred somewhat earlier than the decrease in radioiodine uptake A few patients showed clinical evidence of improvement and 2 were living 20 months after irradiation In 3 patients diabetes insipidus developed None showed signs of panhypopituitarism With radiation levels

(1) C P 18 121 134 F b y 19 8

ressin[8] tannate in oil 3 3 units every other day was al o given On readmission for metabolic studies cortisone was stopped for 2 days and thyroid for 4 days Signs of acute adrenal insufficiency and chemical evidence of complete lack of endogenous adrenocortical hormone developed Premature uterine contractions began 2 months after hypophysectomy and the membranes were artificially ruptured Labor was characterized as strong with unusually long contractions and after 12 hours labor a lb infant was delivered uneventfully without anesthesia During labor the mother received *100* mg hydrocortisone intravenously After delivery thyroid and cortisone therapy were continued at the previous dosage but Pitressin[8] gradually became unnecessary as the diabetes insipidus ameliorated There was no milk secretion On the 11th postpartum day pulmonary infection developed and the condition of the patient gradually deteriorated She died 1 month later of pneumonia

At autopsy adrenals ovarie pancreas and thyroid were atrophic and no pituitary tissue was found Microscopic examination revealed involution of prelactating breasts and atrophy of brea t tissue The only residual carcinoma was a small mass in an axillary node

Placental function was not altered after hypophysectomy as determined by urinary excretion of chorionic gonadotrophin estrogens and pregnanediol Aldosterone excretion serum thyroxin binding protein concentration and the electrophoretic pattern of serum protein were also unaffected Serum protein bound iodine levels studies of corticosteroid metabolism and glucose and insulin tolerance tests indicated deficiency of replacement therapy at 31 weeks of pregnancy Temporary discontinuance of corti one and thyroid therapy were followed by adrenal insufficiency Subsequently there were urinary findings of placental failure and premature uterine contractions There was a drop in serum total proteins with lowered albumin and elevated gamma globulin ratios In the early postpartum period during maintenance therapy with cortisone and thyroid signs of adrenal insufficiency di appeared glucose tolerance became normal and an insulin tolerance test elicited the expected reaction

17 Ketogenic Steroid Excretion in Obese Children before and after Weight Reduction Four cases are described by Harold Cohen[9] (Sheffield Royal Hosp) Urinary excretion of 17 ketogenic steroids in excess of normal for the patients age was initially present in all This became normal after weight reduction due to dietary re triction In 1 patient this phenomenon was observed twice

(9) P t M J 1 696 698 M 1958

nonreactive phase each experiment in which human serum plus estrone and progesterone were injected was controlled by setting up at the same time a group of totally hypophysectomized weanlings which were given prolactin plus estrone and progesterone A satisfactory mammary growth response was induced in all such controls and a similar but less intense response was obtained in all the mice when human female serum was substituted for the prolactin of this hormone combination These experiments suggest that the mammotrophic hormone is produced by the anterior pituitary

► [A major problem in the evaluation of reports dealing with quantitative as ay of lactogenic hormone is the difference in criteria used Bahn and Bates (J Clin Endocrinol 16 1337 1956) have demanded histologic evidence of lactogenic activity which in the case of the pigeon s crop includes cytoplasmic basophilia By their criteria lactogenic hormone could not be detected in the blood or urine of human subjects —Eds]

Effects of Peserpine on Prolactin Content of Rabbit Pituitary Joseph Meites[3] (Michigan State Univ) reports that one intravenous injection of 1 mg reserpine/kg body weight into 5 mature female rabbits which were then killed 1 week later resulted in at least a fivefold increase in pituitary prolactin content over that in 5 controls There was no evidence that reserpine induced mammary growth or lactation Subcutaneous injections of 0 2 mg estradiol daily for 10 days into 6 rabbits elicited 1 week later at least a 10 fold increase in pituitary prolactin content slight growth of the mammary duct system and no milk secretion When estradiol treatment was followed by one intravenous injection of 1 mg reserpine/kg body weight and the 6 rabbits were killed 1 week later pituitary prolactin content was at least 16 times greater than in controls This was accompanied by considerable lobule alveolar development and a limited amount of milk secretion in all 6 rabbits This suggests that the presence of adequate mammary tissue is essential for the prolactational action of reserpine in the rabbit

Reserpine or chlorpromazine failed to induce lactation when injected into mature female rats for 20 days and they did not increase milk production when injected into parturient lactating rats or into goats during the declining phase of lactation Therefore it appears that a species difference

(3) Proc Soc Exp Biol & Med 97 74 44 April 19 8

of 26 000 rad and over 3d 4th and 6th cranial nerve palsies were noted At autopsy pituitary damage was discernible grossly in patients who had received 20 000 rad or over microscopically histologic damage was present in all patients who had received over 20 000 rad Typical of high dosage proton irradiation effects was a pituitary remnant reduced to a membranous lining of the sella 1 mm thick with surrounding normal brain tissue Such an effect is illustrative of the particular advantages inherent in this method

Lactogenic Hormone

Mammotrophic Hormone in Serum of Healthy Women was found in 5 cases by Geoffrey Hadfield and Stretton Young (London)

Method—Totally hypophysectomized weanling male mice were given by subcutaneous injection 0 1 ml human premenopausal serum plus 0 125 µg estrone and 0 75 mg progesterone twice daily for 5 days Mammary growth response was estimated by counting the number of large deeply staining club shaped swellings (clubs) at the duct ends of the mammae and calculating the mean number of clubs per gland No structure having a diameter less than twice that of its parent duct was counted as a club

Mice given serum plus estrogen and progesterone had a mean mammary growth response of 4 clubs/gland whereas untreated intact controls had 0 5 clubs/gland

Administration of estrogen and progesterone alone does not induce significant mammary growth response provided the hypophysectomy is proved to be complete by serially sectioning the sella A similar negative result is obtained when totally hypophysectomized weanling male mice are given prolactin alone for 5 days However the vigor of the mammary reactions observed in these control mice in which a relatively insignificant fragment of anterior pituitary was left behind was impressive especially if the fragment contained cells with eosinophilic cytoplasm

Prolactin plus estrogen and progesterone invariably induces mammary growth response in the totally hypophysectomized small mammal and at optimal dose levels in reactive A G male weanling mice this response is often spectacular To eliminate the possibility in the experiments reported that the mice which had been given human serum were in a

( ) La t 1 568 569 M 1 1958

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(3) Proc Soc Exp Biol & Med 97 742 744 Apr 1958

exists in the ability of these drugs to influence prolactin secretion and perhaps other hormones which regulate mammary growth and lactation

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NEUROHYPOPHYSIS

► Disturbances of water metabolism related to adrenal insufficiency aldosterone excess or administration of other adrenocortical steroid are included in the section on The Adrenal Cortex — Ed

On Nature of Oxytocin and Vasopressin from Human Pituitary Albert Light and Vincent du Vigneaud[4] (Cornell Univ) report comparison of pressor antidiuretic hormones and oxytocin of humans with the hormones isolated from beef and hog pituitaries It has been shown that beef and hog vasopressins differ from one another in one amino acid residue the beef vasopressin containing arginine and the vasopressin from hog pituitaries lysine Arginine vasopressin is the cyclic disulfide of l cysteinyl l tyrosyl l phenylalanyl l glutaminyl l asparaginyl l cysteinyl l prolyl l arginylglycinamide in lysine vasopressin the lysine residue occurs in the place occupied by arginine On the other hand oxytocins from the two sources appear to be identical and differ from vasopressins in having an isoleucine residue in place of phenylalanine and a leucine residue in place of arginine or lysine The ratio of pres or antidiuretic potency is 1 1 for arginine vasopressin and 6 1 for lysine vasopressin

Human pituitaries were desiccated partially purified and finally purified chromatographically The behavior of the purified components on ion exchange chromatography paper chromatography and paper electrophoresis indicated that they possessed oxytocic properties identical with those of beef and hog oxytocin and with those of arginine vasopressin The amino acid composition of oxytocin and vasopressin isolated from human pituitaries revealed that these substances are identified as oxytocin and arginine vasopressin

Etiology of Toxemia of Pregnancy Investigation of Antidiuretic Polypeptide in Urine is reported by Jacques I

(4) Proc Soc Exp Biol & Med 99 69 696 Aug Sept 1958

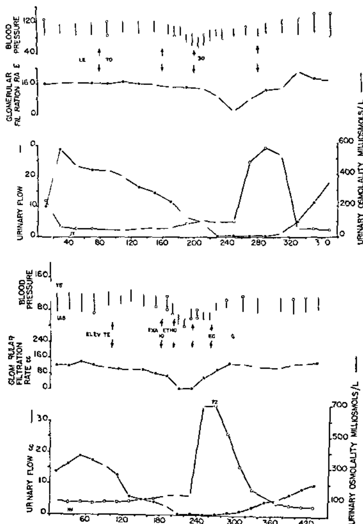
kous and Ingeborg I Dobler Excessive weight gain or sudden dietary changes with salt and water retention may be etiologic factor possibly under the influence of hormonal disturbances in toxemia of pregnancy These disturbances might be excess corticotrophin from the anterior lobe of the hypophysis or excess antidiuretic hormone from the posterior lobe In some patients the disturbances might be related to increased sensitivity to toxemia under the influence of gonadotrophic hormones There is also evidence that placental and renal ischemia are involved as trigger mechanisms and in establishing a vicious circle in producing and maintaining the toxemia

The authors used two dimensional paper chromatography to investigate the presence of an antidiuretic substance in the urine in 21 patients with severe toxemia of pregnancy A polypeptide identical with that described as antidiuretic by others was demonstrated in the urine of all but 3 patients and was present in only 1 of 16 controls This polypeptide was also found in the urines of 1 woman and 3 men with nephrosis and in 2 of 3 commercial posterior pituitary extracts

It was also found that the antidiuretic polypeptide was contained in apparently high concentrations in 3 different commercial preparations of corticotrophin The polypeptide remained in the urine for variable periods after delivery in all 14 patients on whom follow up chromatographic studies were made after clinical signs of toxemia had disappeared In some it was still present weeks or months afterward It is conceivable that it might be present before the development of toxemia and might represent an increased susceptibility of certain patients to toxemia

Production of Hypertonic Urine in Humans in Probable Absence of Antidiuretic Hormone (ADH) has been shown by Charles K Kleeman Morton H Maxwell and Robert Rockney[6] (Univ of California Los Angeles) corroborating animal experiments by others In such studies sharp reduction in the glomerular filtration during water diuresis has been shown to produce hypertonic urine Thus it is conceivable that the primary function of ADH is to allow back dif

(5) S th Af n M J 3 466-47 M y 3 1958
(6) I x Sx E p B l & M d 96 189 191 O t be 1957



T ʙ 5—Effe t of ut d t in Hood p n filt t n te y fl w d o lal ty f p t t w th d t t s n p du (C rt f Kl m C R t P Soc E p B l & M d 96 189 191 Oct b 19 7)

fusion of water when solute is actively reabsorbed in the penultimate portion of the distal tubule permitting delivery of a small volume of isosmotic fluid to the final segment where hypertonic urine may be formed

Method —Two patients aged 25 and 27 with diabetes insipidus

were maintained in positive water balance by glucose infusion After a constant rate of urinary flow was obtained in horizontal position the patients were elevated to 45 degrees for several 20 minute urine collection periods Then hexamethonium was infused intravenously slowly until sustained lowering of the blood pressure occurred After completion the subjects were lowered to horizontal position and urinary collections continued for 6 8 period Osmolality of the plasma and urine was determined by cryometric methods glomerular filtration rate was evaluated from inulin clearance

Elevation from horizontal position to 45 degrees was associated with gradual decline in the glomerular filtration rate and urine flow with slight increase in urine osmolality (Fig 5) Almost simultaneously with the sustained hypotension the glomerular filtration rates decreased precipitously to below 10 cc /minute and urinary flows decreased to below 0 5 cc /minute In both subjects urinary osmolalities rose promptly and strikingly to hypertonic levels (573 and 763 mOsm /L respectively) Normal values were regained subsequent to termination of the hexamethonium infusion and return of normal blood pressure

Reduction of blood pressure to levels barely consistent with continued glomerular perfusion and filtration is apparently shown in this study to be associated with production of hypertonic urine in 2 patients with assumptively total diabetes insipidus The results support animal experiments that suggest that ADH is not essential for production of hypertonic urine

► [This extremely interesting demonstration represents an extension in man of the mechanism demonstrated by the ingenious experiments of Berliner and Davidson (J Clin Endocrinol 36 1416 1957) It raises the theoretical question of whether diabetes insipidus can be diagnosed in the absence of hyposthenuria For practical purposes I believe a urinary specific gravity of more than 1 006 virtually excludes the diagnosis —Ed]

Hereditary Diabetes Insipidus Review of Literature and Resume of Personal Observation are presented by G Bogdanowicz[7] (Univ Saint Pierre Louvain Belgium) Diabetes insipidus is not always acquired but may occur in a congenital and familial form first described by Lacombe in 1841 Since then a number of families have been described some studied by succeeding physicians for up to 7 generations From the literature up to 1956 the author compiled reports on 51 families which include 450 persons with the disease

It has been suggested though not universally accepted

(7) [illegible] 1 18 495 507 July Aug 1957

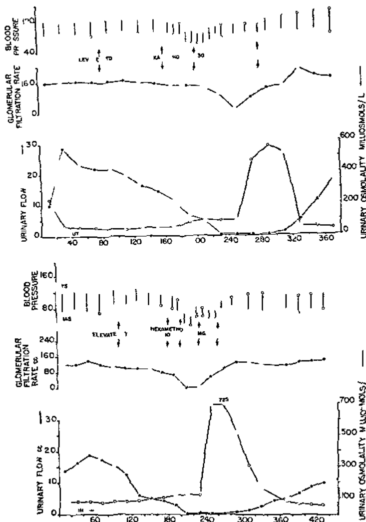


Fig 5—Eff ct f ut l t n blood p n filt t t f kl m n y fl w and m l lty f 2 p t t w th d l t t p d (C rt C R t J oc Soc E p B l & Med 96 139 191 O t 19 7)

fusion of water when solute is actively reabsorbed in the penultimate portion of the distal tubule permitting delivery of a small volume of isosmotic fluid to the final segment where hypertonic urine may be formed

METHOD—Two patients aged 2 and 27 with diabetes insipidus

the nuclei also showed definite but less pronounced cell loss. The anterior commissure showed increase in size and number of astrocytes, indicating reactive gliosis, but myelin stain showed no appreciable fiber loss. The posterior pituitary appeared entirely normal grossly, but with Gomori's aldehyde fuchsin stain no neurosecretory granules were demonstrable. Diagnosis was chronic degeneration of the supraoptic and paraventricular nuclei of undetermined cause.

In a second case, most of the nerve cells in the supraoptic nucleus had disappeared and numerous enlarged astrocytes were noted throughout the nucleus. Moderate cell loss and astrocytic increase had occurred in each paraventricular nucleus. The posterior pituitary was small and atrophic but showed no histologic changes by routine staining technics. The Gomori technic was not used.

In the third case, in which autopsy was done 20 years previously, when the supraopticohypophysial tract and supraoptic nucleus were not studied, the significant finding was atrophy of the posterior pituitary with maintenance of a normal histologic pattern and absence of gross brain lesions.

Blotner considers that idiopathic diabetes insipidus is a system disease due to primary degeneration of the supraopticohypophysial system without obvious reason. Why the degeneration is limited to this area is unknown.

Addison's Disease and Diabetes Insipidus. Report of Case Secondary to Metastatic Bronchogenic Carcinoma 10 Years after Pneumonectomy is presented by Charles A. Kibrando[9] (St. Vincent's Hosp., New York).

Man, 58, had an upper respiratory infection with cough, recurrent severe abdominal pain, excessive thirst and urinary frequency 9 years after right total pneumonectomy for primary bronchogenic carcinoma originating in the right lower lobe (epidermoid carcinoma). He was hospitalized 6 months later because of persistence and recurrence of the complaints, which also included weakness, dizziness and vomiting. Severe sharp pain occurred explosively in the right upper quadrant and the right costovertebral and right loin area, associated with chills and fever that would last about 24 hours. Exertional dyspnea was evident. A chest x-ray showed the mediastinum completely displaced into the right hemithorax. The left lung showed compensatory emphysema. The alkaline phosphatase level was elevated. On discharge 1 month later, he was free from edema and was maintained with hydrocortisone and pituitary powder extract. Diagnosis was adrenal

(9) A.M.A. Arch. Int. Med. 10[illegible]:483, September, 1958.

that three forms of the disease be distinguished Two char acterized by ability to respond well to treatment with ante rior pituitary extract differ in that one form appears to be transmitted by a dominant gene and appears equally in men and women The author describes a family in which 5 gen erations included 10 members with the disease equally di vided as to sex Those free from the disease did not transmit it to their offspring The second pituitary form of the di ease seem to be transmitted by a sex linked recessive gene The third form of the disease has been referred to as nephrogenic and is not influenced by administration of antidiuretic hor mone Though the pathologic anatomy in the pituitary type is consi tent with the suggestion that the disease is due to congenital involution of the supraopticopituitary system re sulting in deficient production of antidiuretic hormone no definite le ion of the pituitary or kidney can be associated with the nephrogenic form of the disease

Symp oms are similar in the three forms polydipsia poly uria and inability to concentrate urinary constituents On the average 24 hour excretion may be 6 12 L though there is great individual variation Limiting fluid intake does not ap preciabl reduce excretion and leads to dehydration and as sociated difficulties Thus infant mortality is high due to the dehydration attendant on other illnes es which limit fluid in take Af er age 3 the life expectancy of the patient is normal however and constitution and physique do not seem to be affected Symptoms may become less severe in later life

► [The que tion arises whether some of the 51 families afflicted with dia betes insip dus which have been reported over the years may not be related In a simil r report of familial sexual precocity in boys (Pediatrics 9 682 1952) a photograph of an x ray bearing initials of one of the patients re sulted in uncovering the fact that these boys were members of the same family originally described by Rush and co workers (Endocrinology 21 404 1937) —Ed]

Primary or Idiopathic Diabetes Insipidus System Dis ease Harry Blotner[8] (Beth Israel Hosp Boston) reviewed autopsy findings in 3 cases of idiopathic diabetes insipidus

In the first case (woman 87) autopsy showed marked loss of nerve cells in the supraoptic nuclei in which hardly any characteri tic nerve cells were present and a considerable degree of localized astrocyte proliferation The paraventricu

( ) Metab l m 7 191 00 M y 1958

periods did not resume A low BMR and a low level of protein bound iodine in the serum indicated severe thyroid insufficiency and the glucose tolerance and Kepler's water tests indicated adrenocortical insufficiency

Treatment was started with 5 mg cortisone orally 3 times daily and 50 mg methylandrostenediol intramuscularly once a week Perceptible subjective improvement occurred within a few days The appetite improved She drank more than before and became more active keeping herself occupied all day She could keep warm Cortisone was gradually increased to 10 mg 3 times daily As the BMR remained —41% after 25 days on cortisone treatment was supplemented with 150 units of thyroid daily 50 mg methylandrostenediol intramuscularly was given every 2 weeks On follow up general condition was satisfactory and she had resumed all ordinary activities Head hair was growing normally She still showed amenorrhea but libido was normal Physical examination showed normal skin and scalp hair but axillary and pubic hair was still sparse Breasts and genitalia remained atrophic Vaginal smears remained unchanged The Kepler water test showed normal water diuresis

The authors suggest that polyuria was due to ischemic necrosis affecting the adenohypophysis Since maintenance of polyuria presumably depends on continued functioning of the anterior lobe explanation of cessation of polyuria may be sought in a rapidly decreasing function of the adenohypophysis and secondarily of the adrenal cortex and thyroid

► [Leaf (J Clin Invest. 31 914 1952) has shown that the fundamental defect of diabetes insipidus can be demonstrated in patients whose pituitaries have been destroyed even though diabetes insipidus may be masked by deficiency of the anterior pituitary In such cases administration of an excretory solute load or of thyroxin desoxycorticosterone cortisone or corticotrophin results in a return of the polyuria —Ed.]

Improvement of Diabetes Insipidus in Hepatitis In fluid metabolism the liver is important in inactivation of antidiuretic hormone (ADH) The affected liver is able to inactivate ADH only to a lesser degree thus a relative ADH preponderance may arise as several reports have noted Therefore partial diabetes insipidus might reasonably be expected to improve during liver diseases The case reported by J Hankiss (Med Univ of Debrecen) is believed to be the first in the literature in which polyuria with diabetes insipidus improved during acute hepatitis

Girl 18 had symptoms of diabetes insipidus after a brain concussion Diagnoses included a hypophysial and hypothalamic lesion diabetes insipidus and hyperthyroidism

At onset of hepatitis the polyuria (8 10 L.) began to decrease

(2) New York J Med 58 19 July 1 1958

in most patients increased output was chiefly obtained by an increase in stroke volume in 2 the heart rate was primarily increased The arteriovenous oxygen difference and mean pulmonary artery pressures at rest and during exercise were normal The mean brachial arterial pressures at rest were normal to high but the group mean was normal During exercise the systolic pressure rose in all patients in whom the cardiac outputs were significantly increased and diastolic pressures rose in 6 fell in 2 and did not change in the 2 without significant increase in output The slight increase in mean pressure for the group was significant Total pulmonary resistance was normal For the group a significant increase in calculated total systemic resistance over normal was found at rest and at exercise A significant decrease in resistance occurred with exercise

The cardiac silhouette was enlarged in two thirds of the patients Catheterization data (slightly higher right atrial and right ventricular end diastolic pressures and the presence of a diastolic dip on the right ventricular tracings) were consonant with the concept that the enlargement so common in hypothyroidism is frequently due to pericardial effusion and not to cardiac dilatation The physiologic protection afforded by the decreased circulatory demands of the hypothyroid state in these patients apparently overshadowed in significance any morphologic changes in the myocardium associated with myxedema

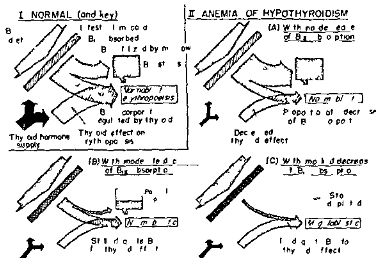
► [These results should be contrasted with those found in hyperthyroidism by Humerfelt and co workers (this YEAR BOOK p 86) —Ed]

Cardiac Disease and Hypothyroidism Complications Induced by Initial Thyroid Therapy In hypothyroidism anatomic changes in the heart may occur They may be tolerated because of concomitant circulatory changes and reduction in total body demands Thyroid therapy reverses these changes and may cause an enlarged heart to function above its physiologic capacity Four patients in whom cardiac complications developed during thyroid treatment were compared with 5 in whom treatment caused no difficulty by Edward L Wallach Glenn D Lubash Burton D Cohen and Albert L Rubin[6] (Cornell Univ)

The complication seemed related to initial vigorous treat

(6) J A M A 167 19 1 19 Aug 16 1958

sorption of radioactive B_{12} was noted with and without added intrinsic factor In 1 patient after 15 months of thyroid therapy weak activity of intrinsic factor appeared A normal Schilling test could then be shown after addition of intrinsic factor In another patient an incomplete hematologic response noted after administration of liver extract (hemo



Fg 8 —D gam f t mn B l jt a d h wng g t l dy m l s l j ct (I) f n p t t w th hypothy d m w th n (IIA) d t (IIB) l ma k d (IIC) t f w th B al pt sec l y t h pcth d m D pl t f body t m B t e wh h m x o ly ft l g t od f al t t bsorpt ec y bef m g l tl t m l l p (IIC) (C rt y f Le thold S L r l \ J M 3 4 53 548 Ap l 1948)

globin 9 5 Gm /100 ml) was considerably improved by addition of thyroid substance therapy (hemoglobin 13 Gm / 100 ml)

The anemia of thyroid deficiency may result from direct and indirect factors The direct influence is more common Thyroid hormone exerts a sustaining influence on the marrow which helps to maintain normal cellularity In hypothyroidism marrow metabolism is often reduced with resultant hypocellularity and decreased need for vitamin B_{12} Conjecturally hypothyroidism may also affect cellular metabolism of B_{12} causing macrocytosis but not megaloblastosis In other instances in an unexplained manner hypothyroidism may lead to moderate or marked decrease in intestinal

had hematocrit values less than 40%. The mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration revealed no gross abnormalities. Reticulocyte counts averaged 0.85%. Red cell fragility was normal. Paper electrophoresis of serum proteins frequently showed an increase in gamma globulin at the expense of albumin, reducing the albumin globulin ratio to about 1.2. There was no evidence of blood loss. In these patients the mean red cell uptake of Cr^{51} in vitro was 54.5% (range 46-64%) and the mean apparent Cr^{51} half life was 13.8 days (range 6-19 days). The viability values were less than 10 days in all cases. Infusion of Cr^{51} tagged blood from 5 of the patients into 5 euthyroid subjects demonstrated an apparent half life of 12.8 days and a viability of less than 10 days. Cr^{51} uptake in vitro was rechecked in 2 hypothyroid patients as soon as they became clinically euthyroid after treatment. Values of 78 and 64% were obtained.

The studies indicate an apparent inborn corpuscular defect which is reversible and may be corrected by administration of active thyroid hormone. The corrective action appears to be mediated through the bone marrow. There is no evidence that a normal hormonal environment (which was produced by infusion of the tagged red cells into euthyroid patients) reversed the effect, however. The evidence seems to indicate a direct effect of thyroid on the bone marrow.

Hypothyroidism with Anemia Demonstrating Abnormal Vitamin B_{12} Absorption was shown in 3 patients by Stanley L. Leithold, Douglas David and William R. Best.[8] Despite the occasional reports of association of pernicious anemia and myxedema and indications that the metabolism of vitamin B_{12} might be influenced by a thyroid deficiency, elucidation of these phenomena have awaited the availability of radioactive vitamin B_{12}. With use of a modified Schilling test 3 of 7 selected patients with hypothyroidism showed abnormal urinary excretion of radioactive B_{12}. Pretreatment with antibiotics did not improve the test in 2 patients so studied. Although their renal function was impaired, it was not seriously damaged and this was not thought to be significantly contributory to the decreased excretion of radioactive B_{12}. Intrinsic factor was absent in the 2 patients. Decreased ab-

(8) Am J Med 24 535-545 Apr 1958

sorption of radioactive B_{12} was noted with and without added intrinsic factor In 1 patient after 15 months of thyroid therapy weak activity of intrinsic factor appeared A normal Schilling test could then be shown after addition of intrinsic factor In another patient an incomplete hematologic response noted after administration of liver extract (hemo

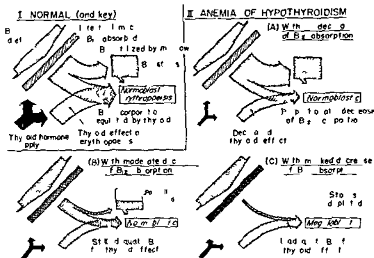


Fig 8—D g m of tam B_{12} al r t nd h w s gg t l b n m l bj ct (I) l p t t w th hypoth d m w th (II) m t (IIB) d m ked (IIC) t t w th B b rt ec ta y t hypoth d m D plet on f body t m B st r wh h may oc f ft f g t d f ad t ab pti n n y bef m g l t d l p (IIC) (Courtesy f Leith ld S L et l A J M 3 24 535 548 Al l 1958)

globin 9 5 Gm /100 ml) was considerably improved by addition of thyroid substance therapy (hemoglobin 13 Gm / 100 ml)

The anemia of thyroid deficiency may result from direct and indirect factors The direct influence is more common Thyroid hormone exerts a sustaining influence on the marrow which helps to maintain normal cellularity In hypothyroidism marrow metabolism is often reduced with resultant hypocellularity and decreased need for vitamin B_{12} Conjecturally hypothyroidism may also affect cellular metabolism of B_{12} causing macrocytosis but not megaloblastosis In other instances in an unexplained manner hypothyroidism may lead to moderate or marked decrease in intestinal

absorption of B_1 Depressed secretion of intrinsic factor or a local intestinal block or both may be present These patho physiologic processes which may participate in the anemias associated with hypothyroidism are summarized in Figure 8

Neurologic Manifestations of Myxedema Stewart N Nickel and Boy Frame[9] (Henry Ford Hosp) reviewed the records of 100 patients with myxedema and found the nervous system to be significantly involved Some of the major and initial manifestations are neurologic in origin (table)

Cerebral function is markedly altered symptoms ranging from anxiety and depression to severe schizoid and manic behavior Hallucinations involving sight sound taste and smell have been noted Organic mental changes are often resistant to average doses of thyroid and as much as 9 gr daily is required by some patients for improvement

In all the cases reviewed the coma of myxedema occurred only during winter suggesting that environmental cold is a precipitating factor In the past the prognosis in coma was poor and in most cases irreversible Availability of the rapidly acting thyroid preparations such as l triiodothyronine which returns the metabolic rate to normal within 24 hours may alter the prognosis in such cases

Abnormal reflexes in myxedema are striking but the changes are not those usually seen in peripheral neuritis Reflexes in myxedema are usually prompt and active with a delayed relaxation phase In peripheral neuritis reflexes are absent or depressed with no alteration in the contraction or relaxation phase The abnormalities in reflexes have been attributed to abnormality in the contractile substance of the individual muscle fibers Subjective sensory complaints in myxedema are prominent but out of proportion to objective findings Subjective weakness is also present but there is little evidence to indicate objective motor deficit Cerebrospinal fluid protein is increased probably constituting another manifestation of the increased capillary permeability in myxedema

One predominant feature of myxedema is the tendency for myxedematous collections to occur in various tissues most commonly about the eyes but also in serous cavities such as the pericardium and pleura Some neurologic signs could

(9) Neurology 8 511 51 Jl 1958

MANIFE TATIONS IN MYXEDEMA SUG ESTIVE OF NEUROLOGIC ORIGIN

	Occurrence Reported	Occurrence Present Study		Occurrence Reported	Occurrence Present Study	Less Commonly Reported Signs
F tigu	100%	8%	Lighth ded s	66%	53%	Com
S bject w k	100%	64%	V rtigo	66%	8%	C l lo
Sl gg h es	91–100%	68%	Dep i	30–50%		D p lo of f t d m ll
D rth	8 –91%	%	Ps hos s	15–50%	5%	F l nei lg
Drow	93%	58%	H ll t n	6–35%	3%	Objecti e m cul w k es
P resth s	40–83%		D cr d us l ct t	4–43%	45%	M ot
Numb es		49%				
Tingl g		36%	D f es	30–41%	31%	
M ry mp m t	66–82%	9%	At i	10 1%	3 %	
Prolo ged l t n of refle es	66%	9%	T n t s	—	9%	
H d ch s	70– 3%	5 %	Object e s ry l s	4%	10%	
			Sl ggi h p pillary eff es	—	9%	
			D plopia	—	5%	

result from similar interstitial accumulation in the nervous system or they might be secondary to changes in cerebral vascular dynamics Another pos ible mechani m is interfer enc with the function of enzyme ystems Thyroxin is a

coenzyme in the important oxidation reduction pathways Any decrease of thyroid will limit the amount of the enzyme available Since important enzymes such as succinoxidase are depressed in the tissue of patients with myxedema and since the nervous system depends on these oxidative enzymes for normal metabolic activity a deficiency would interfere with nervous tissue function

Acroparesthesia in Myxedema Clinical and Electromyographic Study is presented by I P Murray (Univ of Glasgow) and J A Simpson[1] (Univ of Edinburgh) Of 35 patients 26 showed paresthesia of the fingers Both hands were involved in 20 Most patients described the clumsiness of manipulation which is well recognized in myxedema but 8 patients described marked loss of power of finger thumb grip and wasting of the hand suggestive of genuine paresis Evidence of sensory impairment was present in 8 patients invariably on the radial side of the hand In all but 1 sensory changes were confined to the palmar surfaces Motor changes usually consisted of weakness and atrophy of the abductor pollicis brevis and the opponens pollicis muscles

On *electromyography with coaxial needle electrodes* classic signs of partial denervation (spontaneous fibrillation and reduced motor unit activity) were noted in 5 patients with objective weakness These manifestations were confined to the radial border of the thenar eminence except in 1 patient with fibrillation of the 1st dorsal interosseous muscle which sometimes receives fibers from the median nerve No generalized abnormality of nerve conduction was noted but slowed conduction in the median nerve at the wrist was often demonstrated

Clinical and electromyographic findings indicate that the neuropathy is restricted to that part of the median nerve distal to the wrist comparable in every way to the common carpal tunnel syndrome Paresthesia and paresis are probably caused by accumulation of myxedematous tissue under the flexor retinaculum of the wrist

No correlation was noted between presence of neuropathy and severity of myxedema but a clear relation was established between clinical response to treatment of myxedema

(1) La t 1 1360 1363 J 8 1959

and disappearance of acroparesthesia Weight appeared to be of greater significance than degree of hypothyroidism

Hypothermic Myxedema Coma Three Case Reports are presented by Donald W MacDonald (Victoria Hosp Blackpool England) Hypothermic coma is the natural termination of untreated uncomplicated myxedema

Woman 79 was hospitalized in coma She was well until 5 month before hospitalization when she became slowly lethargic and intolerant of cold The skin was smooth and dry with a corpselike coldness Body hair was and had been completely absent since age 18 Rectal temperature was 91 F the pulse impalpable with apex rate 60 and systolic blood pressure 100 mm Hg Serum values were hemoglobin 84 cholesterol 200 and urea 44 mg/100 ml and sodium 152 potassium 5 1 and chlorides 69 mEq/L The ECG showed low voltage complexes in all leads

Treatment consisted of nursing between blankets with no external heat 0 08 mg l triiodothyronine intravenously on hospitalization and 0 02 mg sublingually every 4 hours 50 mg cortisone acetate intramuscularly every 4 hours and 500 000 units of crystalline penicillin intramuscularly twice a day

Temperature rose to 97 F after 12 hours of treatment She received another 0 08 mg triiodothyronine intravenously Temperature was 100 F 36 hours after hospitalization She was then given 50 mg cortisone orally every 6 hours She relapsed into coma 12 hours later but recovered after receiving another 0 08 mg triiodothyronine intravenously She then made an uneventful recovery at first on l thyroxin sodium orally and later on thyroid BP

The fact that the patient responded again to triiodothyronine intravenously after lapsing into coma a second time and that she remained greatly improved on thyroid alone for 3 months shows that this was true myxedema and not hypopituitarism This is the second reported case in which a patient survived over 3 months

Hypothermia in itself is indication for immediate treatment Application of external warmth is unwarranted Thyroid hormone should be given in dosage related to degree of hypothermia Intravenous fluid should be restricted because of danger of myxedema heart failure and occurrence of acute tubular necrosis secondary to hypothermic muscle damage and because physiologic requirement of fluid is small as fluid loss is reduced and metabolic need low

► [It is curious that almost all publications on myxedema coma have come from the British Isles and that all 3 survivors of this complication have been reported from there It is also curious that in the most advanced

) B t M J 1144 1146 N 8 19 8

form of myxedema the only survivals have resulted from administration of heroic doses of rapidly acting thyroidal substances such as triiodothyronine triiodothyroacetic acid and tetraiodothyroacetic acid I know of myocardial infarcts precipitated by this form of treatment but it is possible as MacDonald suggests that in myxedema coma the low temperature result in better tolerance of these agents — Ed]

SUBACUTE THYROIDITIS

Subacute Thyroiditis is a well defined clinical entity but its causes have not yet been sufficiently elucidated In the experience of M Leffkowitz and M Frolich[3] (Petah Tikvah Israel) with 45 patients (27 women) upper respiratory infections did not precede the appearance of local signs of inflammation of the thyroid The patient s description of the sensation in the throat suggested pharyngitis or tonsillitis but the pharynx and tonsils were usually normal

The most important symptoms at onset are lassitude low grade or septic fever and profuse perspiration Later pain develops in the region of the thyroid which may radiate to the mandible and/or toward the ears the thyroid itself becomes tender and swollen

The erythrocyte sedimentation rate is of great diagnostic importance It was considerably increased in all these patients early in the disease and was usually more than 50 mm and frequently more than 100 mm (1st hour Westergren) In the presence of a normal or only slightly elevated sedimentation rate the diagnosis of subacute thyroiditis is most improbable despite suggestive local findings This test also serves as an indicator of recovery or relapse

Low radioactive iodine uptake in the face of normal or elevated protein bound iodine is diagnostically significant The alpha globulin fraction another indicator of protein bound iodine according to recent reports was elevated in 1 of 6 patients in whom it was determined

The most effective therapeutic agent was cortisone though some relapses followed its use

Transitions to other types of chronic inflammatory disease of the thyroid gland such as Hashimoto s disease or Riedel s struma have not yet been observed nor has thyrotoxicosis or hypothyroidism appeared

(3) A ta M 1 O t 1 16 158 159 J ly A g 1957

Thyroid Function and Metabolism of Iodine in Patients with Subacute Thyroiditis Subacute thyroiditi is puzzling in etiology and pathologic physiology Tests of thyroid function are paradoxic Thyroid uptake of radioiodine is characteristically diminished whereas concentration of circulating hormone iodine and BMR may be increased decreased or normal Impaired formation of new hormone and passage of pre formed stores of hormone through disrupted follicular walls into the circulation would explain these results

Sidney H Ingbar and Norbert Freinkel[1] (Boston) verified this hypothesis in studies in 10 patients Each had the usual history and physical findings of subacute thyroiditis viz pain and tenderness over the thyroid gland often radiating to the jaw or occiput pain on swallowing marked asthenia and in some chilly sensations and fever Several had symptoms of hypermetabolism including nervousness increased sweating and weight loss

The 4 and 24 hour thyroidal uptake of radioiodine was greatly decreased during the active inflammatory phase Since 9 patients denied taking any iodine the iodide stores could not have been abnormally large Thus the diminished percentile accumulation of iodine by the thyroid glands was a reflection of diminished synthesis of new hormone Significant quantities of butanol extractable radioiodinated materials were found in the serum of each patient with active subacute thyroiditis indicating that despite the marked reduction in thyroidal uptake of I^{131} some organic iodination presumably thyroidal was occurring In contrast with normal persons the butanol extractable I^{131} concentration declined during the 24 72 hours after administration of radioiodine and despite marked reduction in uptake by the thyroid gland the absolute value of butanol extractable I^{131} was normal or increased These findings probably indicate thyroidal synthesis of small amounts of iodinated materials that are rapidly released from the gland

The thyroid gland can maintain a large store of hormone which can supply hormone despite reduction or complete cessation of hormonal biosynthesis Release from the inflamed gland of abnormally large quantities of pre formed hormone and increase in circulating protein bound iodine

(1) A M A A h I t M d 101 339 346 F b y 1 8

result in hypermetabolism and thyrotoxicosis If synthesis is decreased store become depleted and hypothyroidism ensues

X ray therapy to the gland was followed by rapid and complete return of normal thyroid function within a maximum of 4 weeks Cortisone was symptomatically effective but not as potent in restoring thyroid function to normal

It is suggested that during subacute thyroiditis two principal abnormalities in thyroid function occur diminution though not complete cessation of hormonal biosynthesis and loss of storage function of the gland with passage into the circulation of a variety of iodinated materials—protein proteose peptides and amino acids

Chronology of Events in Development of Subacute Thyroiditis Studied by Radioactive Iodine *P Czerniak and A Harell Steinberg*[5] (Tel Hashomer Israel) studied 10 patients by repeated I^{131} tests The first was performed 10-60 days after appearance of symptoms Tests were repeated every 15 30 days during the first 2 months and then every 2 4 months During observation the patients received no treatment With fairly large variations the natural history of this disease appears to fall into 4 stages (1) The stage of depression lasts about 2 months and is characterized by low thyroidal I^{131} uptake involving the entire gland (not just the inflamed area) with a high urinary excretion of I^{131} There is a normal or high protein bound iodine (PBI) level and decreased production of thyroid stimulating hormone (TSH) Injection of TSH increases the uptake of I^{131} (2) The stage of transition is observed during the 3d month The uptake of I^{131} may be low normal or high with reciprocal changes in its excretion Serum PBI approaches normal (3) Compensation begins at the end of the 3d month and lasts about 4 weeks The I^{131} uptake increases slightly and may often reach elevated levels Urinary excretion of I^{131} decreases The serum PBI decreases usually to a lower level than previously but it may occasionally remain slightly high The TSH production is increased at the beginning and returns to normal at the end of this period (4) Values return to normal during *remission In the 6th or 7th month result* of all tests were normal in the authors cases

(5) J Clin Endocr 17 1448 14 3 December 195

The first stage appears to correspond with release of stored hormone induced by the inflammatory invasion As a consequence the PBI is increased which depresses TSH production and this in turn induces decrease of thyroid I^{131} uptake After utilization of the stock PBI the PBI level declines and TSH production increases inducing increased activity of the thyroid

Thyroid Function in Subacute Thyroiditis may undergo change during prolonged convalescence although essentially all patients eventually return to a euthyroid state Robert Volpe MacAllister W Johnston and Norma Huber[6] (Toronto) evaluated 56 cases of which 11 were severe 15 moderately severe and 30 mild The criteria used were protein bound iodine (PBI) BMR (on a few) thyroidal I^{131} uptake and clinical appearance Four phases of the severe disease could be discerned an initial thyrotoxic phase which subsequently subsided through a euthyroid phase into a hypothyroid state followed by recovery Serum PBI was extremely high in severely ill patients during the toxic phase whereas thyroid uptake of I^{131} was profoundly depressed usually to zero The thyrotoxic phase persisted until the PBI returned to normal range X irradiation appeared to arrest the acute phase of the disease but did not necessarily prevent the subsequent hypothyroid phase Passage through the euthyroid phase might be brief and the patient might subsequently become markedly hypothyroid however the less severely ill patients returned only to the euthyroid phase and did not become hypothyroid In those in whom hypothyroidism developed the PBI fell as low as 0.6 µg/100 ml This hypothyroid phase might last weeks or months but recovery to the euthyroid state occurred in every reported case

In patients with moderately severe cases the thyroid glands were not sufficiently damaged to cause a hypothyroid phase After the PBI fell to a normal range the ability of the gland to take up I^{131} returned to normal without rebound In the 30 milder cases there was neither a hyperthyroid nor a hypothyroid phase though thyroidal uptake of I^{131} was usually depressed for several weeks

X rays (200-400 r) and cortisone ameliorated symptoms

( ) J Cl F docn 1 18 65 78 J y 1958

rapidly but did not avert the phase of temporary hypothyroidism in the extremely severe cases and it is difficult to be certain whether the total duration of thyroiditis was shortened

Regulation of Thyroid Hormone Activity

I^{131} Metabolism in Thyroid Slices of Patients with Various Thyroidal Disorders was studied by Otto P Schumacher F Raymond Keating Jr and A Albert[7] (Mayo Clinic and Found) Slices of thyroid tissue obtained at operation from euthyroid patients and from patients with Graves disease adenoma carcinoma and several types of thyroiditis were studied in a gravity flow system of incubation in a medium of constant composition containing I^{131} The metabolism of I^{131} was expressed in terms of the clearance of I^{131} by the slice tissue medium (T/M) gradients ability to bind iodine in organic form and ability to discharge accumulated I^{131} in response to thiocyanate both in the unblocked state and after blocking with methimazole

Slices of normal thyroid tissue had similar clearance values (0 03 ml /minute/Gm) and T/M ratios (3/4) whether organic binding was permitted or abolished Only half the accumulated I^{131} was protein bound when binding was allowed and the rest of the I^{131} was dischargeable by thiocyanate When Lugol s solution had been administered preoperatively these values were reduced to 50 and 75%

Clearance by slices of exophthalmic goiters was 10 times greater and the T/M ratios 6 times greater than those of normal tissue Protein binding was one third that of normal tissue Thiocyanate induced marked discharge of I^{131} from both blocked and unblocked slices The suppression due to preoperative administration of Lugol s solution was proportionally the same as that noted for normal slices but the suppressed exophthalmic goiter tissue still metabolized 5 8 times as much I^{131} as did suppressed normal tissue

Adenomatous tissue generally metabolized I^{131} in the same manner as did normal thyroid tissue However in 5 cases thiocyanate did not discharge I^{131} from the unblocked slice and in 3 cases thiocyanate was ineffective in both the blocked

(7) J Cl E doc 1 18 354 366 Ap 1 1958

and the unblocked slice Three of 4 thyroid carcinomas metabolized I^{131} in the same manner as did normal tissue in the fourth however accumulation of I^{131} followed the pattern observed in Graves disease though it was less intense Thiocyanate did not discharge I^{131} from slices of the first 3 carcinomas but did so readily from the fourth or hyperfunctioning tissue Slices from patients with Hashimoto s thyroiditis were hyperfunctional with respect to I^{131} metabolism but less so than slices from patients with Graves disease Thiocyanate induced substantial losses of I^{131} from either blocked or unblocked tissue Tissue from 2 patients with granulomatous thyroiditis showed values of I^{131} metabolism like those of normal tissue except for the extremely low content of protein bound I^{131}

Effect of Epinephrine and Norepinephrine on Acute Thyroid Release of Thyroid Hormones was studied by Norman B Ackerman and Walter L Arons[8] (Univ of Pennsylvania) who carried out catheterization of the thyroid vein in dogs and measurement of its protein bound iodine^{131} (PBI^{131}) levels Intravenous administration of epinephrine to 7 dogs and of norepinephrine to 3 dogs increased PBI^{131} levels from 1 5 to 17 1 times the control values within 15 95 minutes Control experiments in 3 dogs showed no significant change in thyroid venous PBI^{131} concentrations in 4 hours

In 2 dogs given thyroid stimulating hormone (TSH) intravenously increases in thyroid venous PBI^{131} levels of 18 9 and 7 4 times the control activities were noted The initial responses occurred within 20 minutes after starting the TSH infusion In 2 hypophysectomized dogs epinephrine infusion was attended with a rise in the thyroid venous PBI^{131} level comparable to that observed in the intact animal These data would indicate that the stimulating effect of epinephrine is exerted directly on the thyroid gland

Preliminary studies in 1 dog revealed that increase of the PBI^{131} level observed in the thyroid vein during epinephrine stimulation was attributable to rise in thyroxin and triiodothyronine *localized by paper chromatography and identified* by scintillation counter Triiodothyronine secreted by the thyroid gland of the dog in response to the acute stress associated with epinephrine elaboration thus may serve as an

(8) E loe 1 gv 62 723 736 J 195

emergency type of hormone Increased thyroxin secretion shown after the epinephrine infusion might also increase *peripheral production of the more potent triiodothyronine* by tissue deiodination mechanism

Effects of Methyltestosterone on Thyroid Function Thyroxin Metabolism and Thyroxin Binding Protein in 3 men and 1 prepubescent girl were studied by Daniel D Federman Jacob Robbins and J E Rall[9] (Nat l Inst of Health) Methyl testosterone 100 mg daily (25 mg 4 times daily orally) for 7 weeks induced a striking fall in the thyroxin binding capacity of the thyroxin binding alpha globulin of serum in all patients and a less striking but consistent increase in the *fractional rate of thyroxin disappearance from the blood* Other findings were a slight fall in the serum protein bound iodine an increase in circulating free thyroxin and an increase in the amount of thyroxin degraded per day There were inconstant effects on the thyroidal and renal clearance of iodide

A fall in concentration of thyroxin binding protein in serum may be responsible for the changes observed A consistent rise in serum cholesterol was also noted during administration of methyltestosterone

Influence of Specific Protein Carrier of Thyroxin on Its Penetration into the Cell was studied by Th Beraud J Cruchaud and A Vannotti[1] (Univ of Lausanne) by measuring radioactivity in the liquid phase and in tissues of rat kidney sections *before and after incubation with* I^{131} labeled thyroxin in a physiologic protein free medium and with addition of normal serum or serum of patients with epidemic hepatitis In the presence of serum protein less I^{131} accumulated in the sections than in controls and diminution was even more marked in hepatic serum which is particularly rich in thyroxin binding protein Addition of Cohn s fraction IV/6 containing $alpha_1$ and alpha globulins to the amount of 6 mg/100 ml produced no change in distribution of radiothyroxin compared with that in controls whereas with 100-400 times that amount (0 5 2 Gm /100 ml) preliminary *experiments showed strong inhibitory effect*

In similar experiments with tissue from animals previously

(9) J Cl I t 37 1024 1030 J ly 1958
(1) Schw m d W h br 88 105 107 F t y 1958

treated with thyroxin carbon tetrachloride or thyroidectomy 3 weeks earlier there were no significant differences from normal tissue As has previously been observed by others in tissue sections mitochondria and red cells uptake of thyroxin by tissue does not depend on the functional state of the gland but on the capacity for physicochemical combination between serum and cell

Liver sections yield similar but less constant results Measurement of inorganic iodine showed that the sections contained little or none at the beginning or after 3 hours incubation and that inorganic iodine in the solution tends to diminish after 3 hours especially in that containing proteins

Radioelectrophoreses of different fractions were less satisfactory on the whole because of the small quantities of thyroxin and difficulties in separation Nevertheless they showed that in the incubation medium at the beginning of the experiment with addition of serum there are 2 radioactive zones one situated between the alpha$_1$ and alpha globulins and the other less well defined which appears to originate with beta globulins a position similar to that of control thyroxin After 3 hours incubation electrophoresis still shows the radioactive zone between the alpha$_1$ and alpha$_2$ globulins while that apparently representing the thyroxin fraction has completely disappeared This probably represents the quantity of hormone which has penetrated into the cell

It is concluded that the serum fraction thyroxin binding protein not only transports thyroxin in the blood but can also inhibit its passage into the cell by indirectly inactivating the hormone Hence penetration of hormones into tissues would depend primarily on the equilibrium between the cellular and extracellular protein fractions that bind thyroxin

► [The lack of biologic activity of protein bound thyroxin is in accord with the observation that the high levels found in pregnancy and after administration of estrogen are not associated with clinical evidence of thyrotoxicosis Conversely the low values following administration of androgens are not associated with clinical hypothyroidism It may be that the more rapid action of triiodothyronine in moderate doses is related to the fact that a relatively large proportion of it remains in the unbound state —Ed]

Metabolism of I^{131} Labeled Thyroid Hormones in Hypophysis and Brain of Rabbit was evaluated by intravenous injection of radiotriiodothyronine and radiothyroxin fol

emergency type of hormone Increased thyroxin secretion shown after the epinephrine infusion might also increase peripheral production of the more potent triiodothyronine by tissue deiodination mechanism

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In similar experiments with tissue from animals previously

(9) J Cl I e t 37 10 4 1030 J ly 1959
(1) Schw z m d W b sch 88 105 107 F b ry 1958

effects of thyroid hormones on the central nervous system see pages 71 and 73 —Ed]

Thyroxin Binding by Serum Protein in Pregnancy and in the Newborn Jacob Robbins and James H Nelson[3] found that the thyroxin binding capacity of serum alpha globulin (TBP) rises in the early weeks of pregnancy to a level about 2½ times that in normal adults (nonpregnant adult average 2.7×10^{-7}M TBP sites for thyroxin) remains essentially unchanged throughout pregnancy and returns to normal within 6 weeks post partum As a result of this rise in TBP the calculated concentration of free thyroxin in serum is significantly lower than that in nonpregnant adults despite a rise in serum PBI

The thyroxin binding capacity of TBP in the newborn is about 1½ that in normal adults and is lower than that in the mother Since the PBI in the newborn is about equal to that in the mother the concentration of free thyroxin is significantly higher This level however is the same as that in nonpregnant adults

Effect of Triiodothyronine Administration on Elevated Protein Bound Iodine Level in Human Pregnancy The increase in protein bound serum precipitable and butyl alcohol extractable iodine during human pregnancy represents an increase in the thyroxin fraction of circulating iodinated amino acids It is possible that the pituitary thyroid servo mechanism is changed the normal pituitary thyroid relation is deranged in a manner similar to that in hyperthyroidism or that thyrotrophin is secreted by the placenta Sidney C Werner[4] (Columbia Univ) tested these hypotheses by giving 75 125 µg triiodothyronine daily to pregnant women in the 2d and 3d trimesters

At all months of pregnancy tested the PBI level decreased by more than 1 µg /100 ml (this is more than the error of the chemical method) but some patients at each month of pregnancy did not respond Larger doses were required in the 3d trimester Uptake of I^{131} was decreased by treatment to the extent seen in nonpregnant healthy women

The clear cut decrease in I^{131} uptake in early pregnancy and in PBI throughout the 2d and 3d trimesters which fol

(3) J Clin Invest 37 153 159 February 1958
(4) Am J Obst & Gynec 75 1193 1196 June 1958

lowed by plasma radioactivity assay autoradiography and chromatography Donald H Ford and Jack Gross[2] (State Univ of New York New York City) found that radiotriiodo thyronine rapidly left the plasma but was delayed in tissue binding perhaps as a result of formation of a plasma triiodo thyronine complex as a precursor of tissue triiodothyronine High organ plasma concentration gradients were achieved with levels as high as 75 1 for the neurohypophysis and 17 1 for the adenohypophysis Radiotriiodothyronine also con centrated heavily elsewhere in the gray matter of the brain particularly in *the region of the paraventricular nucleus* and median eminence Chromatographic analysis of brain tissue showed that the radioactivity was predominantly in the form of triiodothyronine

Distribution of thyroxin was similar but the concentration was much less intense Little activity was detected in the adenohypophysis although the existence of an extravascular thyroxin space there was determined Thryoxin reached peak concentration in the tissues about as rapidly as triiodothy ronine but its level remained more constant with a slower metabolic degradation rate With equal doses about three times as much triiodothyronine as thyroxin was taken up by the tissues This may be related to the differences in biologic activity in the two substances

The localization of these hormones may be related to hypo thalamohypophysial regulatory mechanisms for the secre tion of pituitary hormones This may be associated with production or release of some neurosecretory agent which stimulates thyroid stimulating hormone release—an agent analogous to the hypothalamic factor apparently involved in release of corticotrophin Moreover the distribution of tri iodothyronine in the gray substance parallels that of me thionine when the latter is used as an indicator of sites of active protein formation in the brain It would perhaps indicate the site of thyroid hormone action on the growth and myelination of the brain

► [This is a particularly beautiful piece of work requiring ingenious tech nics and a tremendous amount of meticulous work In this report Gross corrects the earlier suggestion that thyroxin does not penetrate cell He also shows that certain tissues especially the brain and the heart apparent ly are more receptive to triiodothyronine than to thyroxin For the clinical

(2) Endocrinology 6 416-436 Ap 1 1958

cerevisiae were studied with conventional manometric technic by Morris Gutenstein and Walter Marx[6] (Univ. of Southern California). l-Thyroxin significantly accelerated the oxidation of glucose by resting cells of baking yeast at concentrations ranging from 1.3 × 10 to 2 × 10[7] M. Under the conditions of the experiments the hormone did not significantly enhance autorespiration.

l-Thyroxin significantly stimulated respiration of S. cerevisiae at concentrations of the order of 10^{-8} — 10^{-10} M. Lower concentrations had no effect. Autorespiration was again uninfluenced by the hormone.

Inhibition studies indicated that the thyroxin antagonist o-benzyl-3,5-diiodo-dl-tyrosine depressed the hormone-induced acceleration of yeast respiration. In the absence of l-thyroxin the inhibitor did not influence the respiration rate.

The most remarkable aspect of these findings was the unexpectedly great sensitivity of the yeast cell to thyroxin. The hormone had a significant effect at a concentration lower by several powers of 10 than those required for activity of the usual known cofactors of microbial respiration.

► [For a long time students of thyroid logy have sought to delineate actions of thyroid hormones added in vitro. Most attempts met with failure until the preparation of triiodothyroacetic acid. In this and earlier studies from the same laboratory an in vitro action of l-thyroxin is clearly demonstrated, probably because of the type of cell used and also because of the addition of sodium hydroxide which converts l-thyroxin to the soluble sodium salt.—Ed.]

Influence of Thyroid on Adrenal Cortical Function. Ralph L. Peterson (Nat'l Inst. of Health) used cortisol-4-C^{14} to study 8 patients with the classic symptoms, signs and laboratory findings of thyrotoxicosis (Graves' disease) and 7 with typical primary myxedema.

Plasma cortisol levels were normal in most patients with myxedema or thyrotoxicosis. Urine 17-ketosteroids were low in both conditions. Urine corticoids were low in myxedema and were normal or were moderately elevated in thyrotoxicosis.

The urine corticoids returned to normal more promptly than the 17-ketosteroids after treatment of the thyroid disorder. Infused steroids disappeared faster from the plasma in thyrotoxicosis and more slowly in myxedema. Appropri-

(6) J. Biol. Chem. 229:599-60, December, 1957.
(7) J. Clin. Invest. 37:736-743, May, 195

lowed administration of triiodothyronine parallels that of a normal person given the hormone This tends to exclude any abnormal pituitary thyroid relation or the formation and release of large amounts of thyrotrophin by the placenta The data suggest that a *normally responsive pituitary thyroid* relation is present in pregnancy but they do not establish whether the pituitary is secreting at an increased rate thus stimulating the thyroid The best explanation for the elevated PBI of pregnancy is that the binding capacity of the serum carrier proteins is increased for thyroxin

► [In addition to the well known elevation of protein bound iodine level and the newly demonstrated suppression of this moiety by the administration of triiodothyronine thyroid function in pregnancy has now been studied by use of safer I^{132} (see p 78) —Ed]

Salicylates and Thyroid Function II Effect on Thyroid Pituitary Interrelation was studied in man and rats by J Wolff and Frank K Austen The thyroid of salicylate treated patients responds to exogenous thyrotrophin with an *increase in uptake of* I^{131} *an elevation* of the serum protein bound iodine concentration and an accelerated rate of release of I^{131} from the gland

Salicylate treatment leads to partial inhibition of goitrogenesis in propylthiouracil treated rats Salicylate and a variety of its congeners retard the release of I^{131} from the rat thyroid

Salicylate C^{14} does not appear to be significantly concentrated in the pituitary gland hypothalamus thyroid or adrenal

These findings indicate that inhibition of thyroid function produced by salicylate therapy is mediated via an inhibition of thyrotrophic stimulation at a pituitary or higher level The mechanism of this effect has not been elucidated It appears not to be related to the uncoupling of oxidative phosphorylation pyrogenesis chelating ability of ortho substituted phenols or adrenal stimulation

ACTION OF THYROID HORMONES

Stimulation of Yeast Respiration by l Thyroxin The effects of l thyroxin on the oxidation of glucose by resting cells of baking yeast and a pure culture of Saccharomyces

( ) J (I T t 37 1144 115 A g t 19 8

duced to 1 unit the patients showed a significantly smaller increase in plasma 17 hydroxycorticoids than did the controls

It is concluded that in thyrotoxic patients the adrenal cortex is unable to use its potential reserves after physiologic less intensive stimuli

Comparison of Metabolic Effects of Different Thyroid Preparations Rapid onset of increased nitrogen excretion after daily administration of desiccated thyroid and diminution of the catabolic effect immediately on cessation of therapy appeared inconsistent with the concept that this preparation is slow to act and prolonged in its effect Consequently the effects of single large physiologically comparable doses of triiodothyronine thyroxin and desiccated thyroid were studied in 6 myxedematous and 2 euthyroid patients

Laurence H Kyle John J Canary Richard J Meyer and Frances P Pac[9] (Georgetown Univ) report that all three preparations are similar with regard to rapidity and duration of action as judged by such indexes of metabolic acceleration as nitrogen excretion BMR serum cholesterol level and pulse rate In the patients with myxedema identical clinical responses followed treatment with triiodothyronine and desiccated thyroid The differences in response as determined by the various indexes of metabolic acceleration were more pronounced between the subjects than between the compounds Triiodothyronine induced a minimal rise in the serum protein bound iodine level whereas desiccated thyroid induced a rise that was more consistent with other indexes of metabolic acceleration It is suggested that the calorigenic activity of desiccated thyroid depends on its content of or rapid conversion to triiodothyronine and thyroxin

Recent emphasis on the potency of triiodothyronine has engendered the belief that its effects are strikingly different from those of desiccated thyroid and has encouraged the notion that it is more effective The similarities between various thyroid compounds deserve equal stress

► [In this and the following paper the authors have clearly demonstrated that very large doses of all three thyroidal substances triiodothyronine thyroxin and desiccated thyroid produce identical effects and in about the same time I doubt that this is true of the usual doses however inasmuch as the therapeutic administration of thyroid substance or thyroxin to hypothyroid subjects rarely produces any clinical change in the first

(9) J Cl E d.c 1 18 950 9 5 S pt 1 1958

ate therapy for the thyroid disease returned the metabolism of the infused steroids to normal

The rate of synthesis of cortisol was reduced in myxedema and increased in thyrotoxicosis and these alterations in the rate of secretion of cortisol were not associated with a significant change in the size of the miscible pool Establishment of the euthyroid state in these patients returned adrenal cortisol production to normal

These data suggest that there is a homeostatic mechanism mediated through the liver pituitary adrenals which results in decreased synthesis of cortisol in patients with myxedema in whom the rate of removal of cortisol by the liver is impaired and an increased synthesis of cortisol in patients with thyrotoxicosis in whom the rate of removal of cortisol by the liver is accelerated

Function of Adrenal Cortex in Thyrotoxicosis Hyperthyroidism and adrenocortical insufficiency have certain symptoms in common and it has been long known that hyperthyroid patients improve clinically after receiving glycerin extracts L Mikulaj and S Nemeth[8] (Slovakian Academy of Sciences Bratislava Czechoslovakia) studied the response to ACTH in thyrotoxic patients and normal controls

In the first test 25 units of corticotrophin was given in drip infusion over 6 hours The 17 hydroxycorticoids were determined in 24 hour urine specimens the day before the test and on the days after the infusion On the 1st day after the infusion the 17 hydroxycorticoid excretion doubled the excretion on the control day indicating good adrenal function On the 2d and 3d days the controls responded to repeated corticotrophin infusions with increased 17 hydroxycorticoid excretion while patients showed either no increase or a decrease

In the second set of tests the plasma 17 hydroxycorticoids were studied before and after corticotrophin drip infusions When 25 units were infused over 6 hours the 17 hydroxycorticoids in the plasma increased the same amount in the patients and controls When the amount of corticotrophin was reduced to 6 25 units a definite but not significant difference between the corticoid response of the patients and that of the controls was noted When corticotrophin was further re

(8) Schwe[illegible] med Wchschr 88 384 388 Apr 19 1958

After cessation of triiodothyronine administration there was no lag period before the mean cholesterol value began to rise. The return to normal was completed in 10 days.

The mean serum PBI value rose from 5.1 mg. to 20.5 mg./100 cc. by the last day of thyroxin administration. The serum PBI began to fall significantly within 2 days after thyroxin medication withdrawal and returned to control values or below between the 10th to 14th days.

During triiodothyronine medication the mean serum PBI value fell from 5.1 to 3.6 mg./100 cc. and reached myxedema levels 2 days after triiodothyronine administration was stopped. The mean PBI levels then stayed in the clearly abnormal range for 10 days.

Serum inorganic iodine determinations performed simultaneously with PBI determinations showed no significant change.

Use of Triiodothyronine for Reduction of Goiter and Detection of Thyroid Cancer. It has been postulated that goiter size depends on the response of the thyroid gland to pituitary thyrotrophic hormone (TSH). It follows therefore that suppression of this hormone should lead to a diminished goiter size. When sodium levothyroxin or medications containing thyroxin are used for this purpose the serum protein bound iodine (PBI) rises. Triiodothyronine offers two distinct advantages as a pituitary thyrotrophic suppressant: it is several times as potent as thyroxin in its TSH suppressing effect and it exerts this action without accumulating in the circulating blood. Consequently, adequate suppressant dosage of triiodothyronine is indicated by the maximum reduction of the serum PBI.

Paul Starr and William Goodwin (Univ. of Southern California) report that in a series of 36 goiter patients treated with triiodothyronine some reduction in goiter size occurred in all. In over half the estimated gland weight became less than 50 Gm. In many, this reduction in size rendered the goiter invisible. In 4, thyroid tissue became impalpable. Even large goiters were reduced over 50% in size and relief from tracheal pressure and cough occurred in 1 patient. Obvious reduction in size occurred in 30 days in some, but in others was not complete until 9 months. The

( ) Metabolism 92 July 1958

week while triiodothyronine has usually resulted in maximal effects by that time Kyle's paper was presented at the meeting of the Southern Society for Clinical Research in New Orleans Jan 25 1958 at which time he made clear his desire to counteract the "extravagant praise and propaganda" regarding the alleged immediate and intense effect of triiodothyronine To do this he will I think have to demonstrate similarity of effect of the usual doses of these agents It is also noteworthy that no adverse effects occurred in either of these two series or in that of Selenkow and Asper (J Clin Endocrinol 15 285 1955) despite the fact that all three groups were giving tremendous amounts of potent preparations to patients with severe myxedema —Ed]

Thyroxin and Triiodothyronine in Excessive Dosage to Euthyroid Humans William H Beierwaltes and George I Ruff[1] (Univ of Michigan) gave these hormones to 12 euthyroid healthy male college students in dosage large enough to elevate the BMR and depress the serum cholesterol One drug was given first to 6 subjects and the other was given first to the rest The drug was then stopped abruptly All were allowed to recover then were given the second drug in excessive dosage This drug in turn was abruptly discontinued and the subjects were allowed to recover Throughout the experiment BMR serum cholesterol and serum protein bound iodine (PBI) determinations were followed closely

With thyroxin therapy the mean BMR rose from −3 8% to +11 6% or 15 percentage points by the time thyroxin was stopped The BMR then continued to rise to +24% at 2 and 4 days after cessation of thyroxin administration and was still at a value of +10% at 10 days after cessation With triiodothyronine administration the mean BMR rose higher and was at maximum by the last day of medication The maximum mean rise in BMR after triiodothyronine was not as great as the maximum rise after thyroxin The mean BMR value had fallen to premedication control level by the 6th day after triiodothyronine withdrawal

The mean serum cholesterol fell 71 mg/100 cc (34%) from the control premedication mean value during thyroxin administration It continued to fall through the 8th day after thyroxin withdrawal but started to rise by the 10th day

As with the BMR response cholesterol response to triiodothyronine differed from the response to thyroxin in that the mean serum cholesterol value showed a response of greater and maximum magnitude by the last day of medication

(1) A M A Arch Int Med 101 69 576 March 1958

treatment with toxic doses of thyroid hormones should be removed surgically —Ed.]

Electroencephalography in Thyroid Disorders was studied in 70 patients by J. Vague, H. Gastaut, J. L. Codaccioni and A. Roger[3] (Marseilles). In all 19 patients with simple goiter a posterior alpha rhythm was registered—8-10 c. in 7, 10-12 c. in 6 and over 12 c. in 6. Rolandic activity was evident in 15 and was of beta frequency usually occurring in surges and associated in 11 with a rolandic arcate rhythm reacting to somesthetic stimuli. In 2 patients with posterior rhythm of a frequency of over 12 c. beta rhythms were not confined to the rolandic area but were generalized giving the tracing an appearance of rapid dysrhythmia.

Theta activity was noted in 7 patients, 2 of whom were aged under 25. In 1 patient slow posterior waves reacting to opening of the eyes were superposed on alpha activity. Posterior rhythm of 4 c. was registered in 4 patients. Reaction to intermittent light was normal in all but 5, 3 of whom showed an oculoclonic response and 2 appearance of posterior wave points. In 1 patient with neuropathy and thyroid hyperplasia therapy with sedatives and thyroxin resulted in disappearance of slow posterior waves and slowed the base rhythm to 10 c. but beta and arcate rolandic activity persisted. On the whole the EEG in these patients was normal. Rolandic rhythms were more pronounced than usual and the number of oculoclonic responses appears significant as does the rhythm of 4 c. in 2 patients, for this is rare in the general population.

In hyperthyroidism base rhythm was slow—under 8 c. in 3, 8-10 c. in 15, 10-12 c. in 17 and over 12 c. in 7. In 31 of 42 patients rolandic activity was pronounced with very wide beta rhythm (Fig. 10) associated with spurts of arcate activity in 25. In 18 rapid posterior rhythm was associated with generalized beta spurts; theta activity was noted in 18 and in 10 slow posterior waves were superposed on alpha activity. Posterior rhythm of 4 c. was evident in 3 patients. Only 1 oculoclonic response to intermittent light stimulus occurred.

In a patient in whom cranial trauma resulting in loss of consciousness was more emotional than physical the EEG pattern was complex (Fig. 11). The posterior rhythm was

(3) Ann. d'endoc. 18:996-1009, Nov.-Dec., 1957.

usual initial dosage of triiodothyronine was 25 µg twice a day with increments every few weeks as indicated by failure to lower the PBI

Chronologic representation of successive increases in dosage and decline in serum PBI and goiter size in a woman

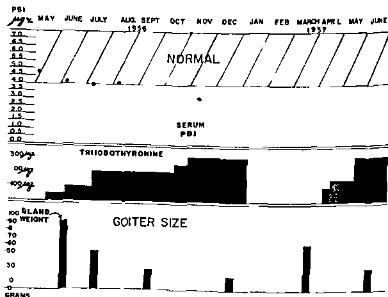


Fig 9—S e ncreases n l ge d d cl e n m PBI d go te s mult l w th po tm p l go ter At abo t ag 45 h had sl ght thy o l e l g m t a m d t b llo d g t S m PBI th n w 3 8 3 9 a d 4 µg /100 ml but thy d m d t n w g e M p occu d t g 49 V g l bl d g t ag 51 l d t pa hy t t my wh n m l l x m t h d 90 Gm mult nod l g t She h d h t ry f mild hyp rt o T tm t edu ed thyr d w ght t 20 Gm when g t was lm t imp lp bl (C u t y f St P d Coodw W M t b l m 7 287 29 J ly 1958)

with postmenopausal goiter are shown in Figure 9 Note that with interruption of dosage there was recrudescence of the goiter In 1 patient a nodule that did not regress while the rest of the thyroid became impalpable was found to contain an encapsulated follicular adenocarcinoma of the thyroid

► [My good friend Paul Starr has been trying to put surgeons out of business for some years now first by treating Graves disease with radioiodine and now by reviving the early observations that the proper treatment of goiter is thyroid In the case of simple goiter I agree with him wholeheartedly I think it important to bear in mind that usually administration of sufficient thyroid hormone to produce mild toxicity is required to cause involution of simple goiter and certainly nodules which persist during

treatment with toxic doses of thyroid hormones should be removed surgically —Ed]

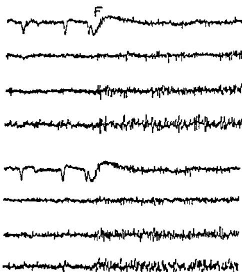
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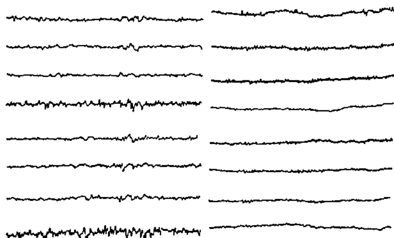
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(3) A doc 1 18 996 1008 N Dec 1957



19 F) 10 (C te f \ g J t I \ n be I 18 996 1018 \ D



19 F) 11 (C n f \ g J t I \ ic I 18 996 1009 \ D

9 c and the rolandic region showed arcate and beta activity There were bursts of theta waves at 5 c generalized and associated with certain bisynchronic anomalies i e delta monorhythmic waves augmented during hyperpnea After treatment (Fig 11) posterior and rolandic rhythms were not changed but theta bursts diminished and delta waves disappeared

In 6 other patients clinically improved after therapy basic rhythm remained the same or was slowed Among 5 with arcate rolandic rhythm and marked beta rolandic wave treatment caused disappearance of the waves in 2 slowing and decrease in arcate rhythm in 1 and considerable decrease in beta activity in 1 in whom arcate rhythm was not changed In 2 of 3 patients treatment caused disappearance of slow posterior waves

In only 1 of 9 patients with hypothyroidism was the alpha rhythm below 8 c It was 8 10 c in 5 and 10 12 c in 3 Rolandic activity was registered in 3 2 showed arcate rhythm Theta waves were pronounced in 7 One patient over 25 had slow posterior waves Reaction to intermittent light was abnormal in 3 1 showed an oculoclonic response In 4 patients significant EEG anomalies were noted 2 showed transmitted activity of pointed wave type and 2 showed delta waves in rhythmic bursts In all 5 showed definitely pathologic tracings There was also a large amount of beta activity in this group One patient presented EEG findings typical of hyperthyroidism while in a state of minor posthyperthyroid myxedema

Contribution to EEG Study of Endocrine Syndromes including hypoglycemia thyroid disorders tetanie adrenocortical disturbances endocrinopathies of hypothalamic origin acromegaly and cranial hyperostoses of neuroendocrine origin is presented by F Thiebaut F Rohmer and A Wackenheim[4] (Strasbourg France) Various endocrine disturbances may alter the activity of the brain and study of the changes offers a new approach to relations between cerebral function and endocrine mechanisms The are of theoretical and practical importance

The EEG changes during artificially stimulated hypoglycemia in normal subjects vary Some persons show hyper

(4) EEG Clin Neurophysiol & Cl N ph 1 10 1 0 F t 19 8

sensitivity with even a slight decrease in blood sugar This hypersensitivity may be pathologic manifested in clinical phenomena difficult to recognize without the EEG The relation of hypoglycemia to convulsive pathology gives prime importance to the study of EEG changes due to artificially stimulated hypoglycemia In repeated hypoglycemic episodes resulting from insulin treatments (Sakel method) or from hyperinsulinism two types of EEG changes can be demonstrated those immediately reversible on administration of glucose and those expressing organic damage

The EEG changes differ widely in hypo and hyperthyroidism In myxedema slow monomorphous rhythms are seen whereas in hyperthyroidism rhythms are rapid with a tendency to paroxysmal discharge Differential diagnosis between primary and secondary hypothyroidism is sometimes possible by EEG The EEG disturbances react to thyroid therapy in congenital and acquired myxedema

Three types of tetany can be differentiated by EEG tracings (1) hypocalcemic convulsive tetany due to parathyroid deficiency (2) neurogenic tetany and (3) a miscellaneous group of spontaneous and hypoparathyroid tetanies with milder clinical symptoms Electric activity of the brain in tetany is usually abnormal and sometimes greatly disturbed Anomalies are proportional to clinical signs and in the individual patient to calcium levels The EEG is always abnormal during seizures or contractions Patients with neurogenic tetany show specific epileptogenic EEG changes that respond well to treatment of the tetany The EEG changes typical of epilepsy have not been observed in convulsions due to parathyroid deficiency

In adrenal syndromes EEG disturbances are variable and inconsistent The EEG findings in hypercorticism and acromegaly are similar Study of 4 patients with chronic adrenocortical insufficiency during treatment indicated that significant EEG changes during hyperpnea are produced by desoxycorticosterone acetate treatment

Among endocrinopathies of hypothalamic origin two EEG patterns were observed in the adiposogenital syndrome (Fröhlich s syndrome) one apparently correlated with postencephalitic manifestations and the other with degenerative lesions Few changes were noted in diabetes in

sipidus The EEG changes in hypothalamic amenorrhea supported Reifenstein's hypothesis of the association with endometrial atrophy

In acromegaly EEG findings were often useful in evaluating the extent and rate of progression of a pituitary adenoma In neuroendocrine disturbances associated with cranial hyperostosis EEG changes are frontally situated when the osseous hypertrophy is mainly frontal and diffuse when hyperostosis is generalized

The EEG signs are often of diagnostic value in endocrinopathies provided it is kept in mind they are not specific patterns and that they should be interpreted in relation to clinical manifestations particularly clinical and EEG progression

Thyroid Function Tests

Use of Iodine[1] for Thyroid Function Tests was studied by K F Halnan and E E Pochin[5] (Univ College Hosp Med School London) The radioiodine isotope I^{132} has a half life of 2.3 hours and gives a substantially lower total dose to tissues than does the commonly used isotope I^{131} (half life 8 days) Though I^{132} has much higher energies of beta and gamma emissions than does I^{131} and so gives higher dose rates the total dose from I^{132} is much lower because of the much shorter half life The higher mean energies emitted during decay of I^{132} also imply that most counting systems will have an equal or higher sensitivity to I^{132} than to I^{131} Compared with I^{131} I^{132} allows reduction of dosage of about 40 100 times to the thyroid and of 3 to 4 times to the gonads Its use is therefore most desirable when radioiodine investigation of children and pregnant women is needed

Another advantage of I^{132} is that because of its rapid decay tests may be repeated at short intervals reliably and conveniently since the thyroid radioactivity due to any test will fall to less than 1% of initial value after 24 hours The rapid decay also involves use of a short term test such as the neck thigh ratio measured 2 hours after an oral dose This ratio is about proportional to the thyroid clearance rate of plasma

(5) Brit J Radiol 31 591 588 November 1958

iodide and its use does not require exact measurement of the given dose measurement of a standard or decay calculations An early measurement such as at 2 hours should differentiate better between hyperthyroid and euthyroid patients than measurement at 24 hours becau e uptake in the hyperthyroid gland is more rapid and reaches a higher maximum

Figure 12 shows the range of results with randomly e

I g 12 —N k th gh r t h r ft I ally n I ly s l t l p t t w th l l thy t cos (o) t thy o d me d wome (les) d p t t w th total thy d bl t on (k tal l) M n t h wn f ach g p w th g f tw th S D (ow) C t y f H I K E d Poch F E Br t J R lol 31 581 588 No mber 1958)

lected groups of 29 clinically thyrotoxic patients (mean neck thigh ratio 43±22 S D) 42 normal controls (mean ratio 3 0±1 0 S D with 3 3±0 9 in 11 females and 2 9±1 0 in 31 males) and 11 patients after total thyroid ablation (mean 1 5±0 2) Thus differentiation between results on thyrotoxic and euthyroid subjects is good but diagnosis of hypothyroidism is not as good

Pituitary thyrotrophic hormone (10 units) was given intramuscularly to 2 controls and 2 patients with nontoxic goi

ter and I^{13} neck thigh measurements were made frequently over the next 2 days In all maximal increase in uptake was demonstrated at about 24 hours after injection Day to day tests on 10 controls revealed that the neck thigh ratio was approximately doubled on the day after injection with a return to normal in a few days This effect was not prevented by simultaneous administration of thyroxin

That injection of thyrotrophic hormone had no effect in hypothyroid patients without signs of hypopituitarism was confirmed in 10 instances If thyrotrophic hormone is injected into a patient with hypothyroidism secondary to pituitary deficiency there is usually a response unless the pituitary deficiency is long standing and the thyroid presumably atrophic

► [The use of therapeutic doses of any radioiodine in pregnancy is certainly contraindicated though Chapman and others have described normal children born of mothers who had received this treatment during unsuspected pregnancy That the fetus can take up radioiodine even in the 1st trimester is indicated by Goldstein (this YEAR BOOK p 9?) The contribution of the next 3 papers is evidence of efficient measurement of thyroidal uptake of iodine by means of the short lived isotope I^{13} whose emission is more readily counted than that of I^{131} so that small amounts can be given From their calculations the authors of the next 3 reports suggest that this isotope may be more suitable in the cases of pregnancy and lactation in children or where serial tests are indicated It is not sufficiently economical or available for routine use and will therefore probably not replace I^{131} —Ed]

Use of Iodine[13] in Studies of Thyroid Function is reported by A W G Goolden and J R Mallard[6] (Hammersmith Hosp London) For routine diagnostic tests of thyroid function I^{131} has proved satisfactory When serial tests are required an isotope with a shorter half life is preferable After distillation I^{13} contains a small impurity of I^{131} which arises from the decay of $Te^{1\,1}$ (an isomer) which is present in the Te^{13} solution The ratio of I^{131} to I^{13} in the distillate depends on several factors

When serial measurements of thyroidal uptake of radioiodine using I^{131} and I^{13} were made in thyrotoxic patients comparable measurements were obtained with both isotopes Urine excretion and 6-hour thyroid uptake measurements were made on 17 normal males 4 times during 1 week The measurements suggested the presence of a physiologic variation which gives rise to a standard deviation of 14 4 % in

(6) Brit J Rad 1 31 589 595 November 1958

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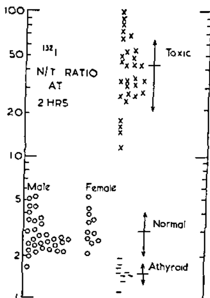


Fig 1 —Neck thigh t 2 h ft I all 1 mly s l t I p t t w th l l th ot (e) thy o d m n nd wom (l s) d p t e w th t t l thy d bl t n (h t l l) M n t h wn f r l g p w th a nge f tw ce th S D (ow) C t y f H I K E d P h E E B t J Rad ol 31 581 588 N mb r 1958)

lected groups of 29 clinically thyrotoxic patients (mean neck thigh ratio 43±22 S D) 42 normal controls (mean ratio 3 0±1 0 S D with 3 3±0 9 in 11 females and 2 9±1 0 in 31 males) and 11 patients after total thyroid ablation (mean 1 5±0 2) Thus differentiation between results on thyrotoxic and euthyroid subjects is good but diagnosis of hypothyroidism is not as good

Pituitary thyrotrophic hormone (10 units) was given intramuscularly to 2 controls and 2 patients with nontoxic goi

Halnan[7] (Univ of London) I^{132} was used since radiation to the test subject is much lower than with I^{131} The former has a half life of 2 3 hours Calculations showed that a dose of 6 µc I^{132} would give a radiation dose of less than 0 2 rad to the mother s thyroid 0 01 0 06 rad to the fetal thyroid and less than 0 001 rad to maternal or fetal gonads Thyroid up take was measured in terms of the ratio of radioactivity in the neck and thighs of each subject measured simultane ously Preliminary tests showed no significant difference be tween results with I^{132} and I^{131} with the apparatus used

The mean neck thigh ratio during pregnancy and 1 week after delivery was significantly higher than 6 weeks after de livery Administration of 40 µg sodium 1 triiodothyronine twice daily for 1 week depressed the neck thigh ratio whereas 1 intramuscular injection of thyrotrophic hormone about doubled it in both pregnant and nonpregnant women

The results suggest an increase in thyroid activity during pregnancy which cannot have been caused by iodine uptake in the fetal thyroid or by iodine secretion in milk The thy roid itself appears to be neither more nor less sensitive to pituitary stimulation The rise in radioiodine uptake in preg nancy could be secondary to iodine deficiency or to increased hormone output The rapid restoration to normal uptake during the puerperium makes iodine deficiency unlikely The possibility of increased hormone output is confirmed by the known increase in protein bound iodine during pregnancy The normal response to triiodothyronine and thyrotrophic hormone administration implies that the increa ed thyroid activity probably is mediated by thyrotrophic hormone The most likely reason for the increased hormone output appears to be estrogen inhibition of tissue metabolism

Studies of Children Born to Women with Thyroid Disease Interrelations between thyroid function of the pregnant woman and of the fetus depend not only on the degree of per meability of the placenta to thyrotrophic hormone to thy roxin like iodine compounds and to compounds with anti thyroid activity but also on fetal thyrotrophin productivity and fetal thyroid activity Evelyn B Man Benjamin A Shaver Jr and Robert E Cooke[8] (Yale Univ) present data

(7) Cl S 17 31 90 1958
(8) Am J Obst & Gyn 75 728 741 Apr 1 1958

day to day neck uptake measurements and 59% in urine measurements

As I^{13} is particularly useful when serial tests of thyroid function are required the authors used it to study the alteration which occurs in thyroid uptake after discontinuing antithyroid drugs Patients treated for thyrotoxicosis with radioiodine at the authors institution are usually given preliminary treatment with carbimazole which is discontinued 48 hours before hospitalization and a pretherapeutic test dose of I^{131} given on admission This allows sufficient time for the inhibitory effect of drugs of the thiouracil group to wear off The first test was made 4 hours after the drug was stopped The test curve showed a high initial accumulation of radioiodine due to the augmented trapping mechanism and thereafter a negative slope After 24 hours the thyroid had escaped from the inhibitory effect of the drug and uptake was high Further tests made over 5 days showed little further change after the first 24 hours Similar results were obtained in other patients who had been maintained on carbimazole Serial tests were carried out also on patients maintained on potassium perchlorate The inhibitory effect of perchlorate persisted considerably longer than that of carbimazole

Simultaneous measurements of the rates of entry of radioiodine into the thyroid and its release from the thyroid as radiothyroxin can be made only by using 2 isotopes of iodine with different half lives By a double isotope technic the mode of suppression of thyroid function in response to administration of triiodothyronine was studied Thyroid function was determined initially after an intravenous dose of I^{131} by conventional radioiodine tests and biologic half life was obtained by plotting values of thyroidal radioactivity corrected for radioactive decay on semilogarithmic graph paper At intervals during the observation uptake of radioiodine after intravenous doses of I^{13} was measured

The authors have not used I^{13} in routine assessment of thyroid function and believe that it is unlikely to replace I^{131} entirely in standard diagnostic work It has however proved useful in experimental work on thyroid metabolism

Radioiodine Uptake of Human Thyroid in Pregnancy at 12 24 and 36 weeks was measured in 21 patients by K T

O Kumer[9] (State Hosp Klagenfurt Austria) performed radioiodine tests on 59 patients aged 20 85 from mountainous areas deficient in iodine About 25% of the patients had no thyroid disease On arising in the fasting state the patients received 40 100 μc I^{131} by mouth No patient received more than 40 μg After 2 hours 25 cc venous blood was drawn After 24 hours uptake was determined over the thyroid gland and after 48 hours a second blood sample was drawn Patients with no thyroid enlargement or other thyroid pathology had an average 24 hour uptake of 75% with variation between 42 and 99% The 2 and 48 hour plasma values varied greatly

Uptake values in hyperthyroidism and in euthyroid goiters were not significantly higher than those obtained over normal thyroid glands The 48 hour plasma values could not be used for diagnosis of hyperthyroidism in patients with goiter if the 2 hour plasma value for radioiodine was abnormally low Thus in areas with extreme iodine deficiency diagnosis of euthyroid goiter has to be made clinically and supported by normal BMR values Malignant goiters showed reduced radioiodine uptake as did myxedematous goiters In diagnosis of myxedema uptake studies are of great help

► [The foregoing paper confirms the assumed avidity for radioiodine of thyroid glands of persons living in goiter areas It is therefore not feasible to use this test for the differential diagnosis of goiters in these regions The administration of iodine corrects this avidity as can be seen from the following report —E 1]

Iodide Repletion Test for distinguishing iodine deficiency from mild thyrotoxicosis is discussed by Craig D Burrell and Russell Fraser[1] (Postgrad Med School London) To correct for any possible iodine deficiencies 10 mg /day potassium iodide is given for 2 weeks The radioiodine test is performed 4 weeks later

This test applied to untreated patients gave the following results (1) persistently avid uptake in 24 of 25 patients with mild thyrotoxicosis (2) persistently avid uptake in 2 of 3 patients with ophthalmic Graves disease (3) normal uptake in 29 of 30 patients with anxiety states (27 with nontoxic goiters) in whom thyroid uptake was initially high and (4) normal or low uptake in all of 11 patients with nontoxic goiter

(9) Wien klin Wchnschr 0 99 103 Feb 7 1958
(1) Q t J Med 6 5 9 O obe 19

on 19 infants born to 5 treated hyperthyroid women 4 treated hypothyroid women and 9 women clinically euthyroid when not pregnant but given desiccated thyroid during pregnancy because of prolonged sterility or previous abortion The thyroid status of the mothers and infants was evaluated clinically and by measurements of butyl extractable or thyroxin like iodine of the serum of maternal and cord blood at delivery and of the infants at ages 2 and 5 days

The hypothesis that untreated euthyroid women during pregnancy have increased tolerance for thyroxin like iodine in blood plasma i upported by previou ly published data

Hyperthyroidism of the woman usually decrea es in e verity during pregnancy Of the 5 hyperthyroid women in thi series 4 were clinically euthyroid during pregnancy after the daily intake of propylthiouracil had been greatly decreased or stopped Other investigators have recommended reduction of propylthiouracil during the la t trimester and administration of desiccated thyroid to any woman in whom hypothyroidi m develops as a re ult of surgical or medical treatment for hyperthyroidism during pregnancy Even tran ient maternal hypothyroidi m mu t be prevented during pregnancy to prevent fetal abnormalities For the hypothyroid woman the daily intake of de ic cated thyroid may need to be increased during pregnancy thi was nece ary for 2 of the 4 in this series

To avoid possible hypothyroidi m in the woman and a goiter in the fetu excessive do age of iodides mu t be avoided during pregnancy Conver ely for many year intake of inorganic iodine in moderate amount has been recommended for the pregnant woman in endemic goiter area and for the woman with thyroid enlargement or hyperthyroidi m Of the 5 hyperthyroid women in this group 4 received uch controlled therapy with inorganic iodine without demonstrable injury to the fetus

Diagnosis of Thyroid Diseases by Radioiodine with Special Reference to Iodine Deficiency It has been suggested that determination of radioactive iodine uptake by the thyroid gland in combination with urinary excretion studies i in ufficient for a se sment of thyroid function in iodine deficient areas such as certain parts of Au tria

the basophils The mean absolute basophil count in 9_ healthy subjects was 32 8±18 (S D)/cu mm

In most cases of thyrotoxicosis the absolute basophil count is markedly decreased in myxedema increased and in struma simplex within the normal range After methylthiouracil therapy the basophil count is markedly increased in thyrotoxicosis There is good correlation between the basophil count and decrease in serum protein bound iodine (PBI) or BMR and improvement of symptoms In thyrotoxicosis after treatment with dried thyroid the basophil count shows no change or only slight increase

In myxedema after treatment with dried thyroid or thyroxin the basophil count is markedly decreased Fair correlation is noted between the decrease in basophils and increase of serum PBI or BMR and improvement of symptoms

In nephrosis the basophil count increases to above the mean absolute basophil count of normal subject Dried thyroid treatment causes the basophil count to decrease in nephrosis and in euthyroid patients but when treatment is discontinued it is rapidly restored

There is good correlation between the basophils of the blood and thyroid function indicating that estimation of the basophil count is valuable as a thyroid function test

Hyperthyroidism

Comparison of Radioiodine Tests in Diagnosis of Hyperthyroidism is presented by A W G Goolden[4] (Hammersmith Hosp London) Tests of thyroid clearance urinary excretion and a plasma protein bound iodine^{131} (PBI^{131}) were compared in a series of 70 patients who were treated with radioiodine and in 50 untreated patients All three tests were efficient in untreated patients although not many of these had mild hyperthyroidism The thyroid clearance test was more reliable than the urinary excretion test in the treated patients

The values for plasma PBI^{131} at 48 hours were high in euthyroid and hyperthyroid patients after treatment with radioiodine This test cannot be used to diagnose residual hyperthyroidism in treated patients

[Here as usual evaluation of thyroid function tests is made in patients

(4) B t J R d 1 31 433 436 \ g t 1958

who showed an initially high thyroid uptake and also in other euthyroid patients tested

The test applied after previous prolonged administration of antithyroid drugs showed (1) persistent avidity in all of 6 *treated thyrotoxic patients who later relapsed (2) normal* uptake in 9 of 10 treated thyrotoxic patients who remained in remission (3) normal uptake in 5 of 7 patients with goitrous myxedema due to antithyroid drugs given for other reasons and a value much nearer normal in the other 2

The iodide repletion test is recommended when the simple radioiodine test reveals an unexpectedly avid thyroid uptake of dubious clinical significance and also for testing patients who had been receiving antithyroid drugs

Test of Thyroid and Pituitary Function Using Thyrotrophin is described by R F Fletcher and H Besford (*Queen Elizabeth Hosp Birmingham England*) The uptake of I^{131} in the thyroid at 24 hours was used to measure thyroid function before and after a single injection of 10 USP units of thyrotrophin in 76 patients In normal persons iodine uptake after thyrotrophin injection always tended to be 50-60% regardless of the initial level In hypopituitarism the uptake increased at least 1 5 times after thyrotrophin was given whereas in primary myxedema there was no response

On the basis of the findings in this study criteria may be suggested for planning and interpreting future tests If the initial uptake of iodine at the neck at 24 hours is below 30% it should increase at least 1 5 times after thyrotrophin if the thyroid is normal Such a result in an untreated patient is suggestive of hypopituitarism If the initial uptake is 30 50% the uptake after thyrotrophin should be 45% or more if the thyroid is normal If the initial uptake is over 50% the response to thyrotrophin may be small or absent even in the normal thyroid and the test need not be continued

Relationship between Level of Circulating Basophil Leukocytes and Thyroid Function was studied by Satoshi Inagaki[3] (Niigata Univ) who devised a new direct counting method for these cells in the circulating blood A lead acetate solution was used for fixing and toluidine blue for staining

(2) Cl n Sc 17 113 1 0 1958
(3) Act Iocri 1 6 447-488 Decembe 1957

Hyperthyroidism in Patient with Pituitary Chromophobe Adenoma and Fragment of Normal Pituitary is reported by Sidney C Werner and Wellington B Stewart (Columbia Univ) Since it is not established whether Graves disease is due to an excess of pituitary thyrotrophin or to other mechanisms this case is of interest

Many findings support the view that the patient a woman 59 had hyperthyroidism The 24 hour thyroid I^{131} uptake was 65% and serum precipitable iodine was *7 9 μg /100 ml* (normal 3 5 7 5 μg /100 ml) The thyroid was enlarged The patient had intractable heart failure with a huge heart but no evidence of intrinsic cardiac disease The terminal episode with a rise in temperature and death after 12 hours clinically suggested thyroid storm though adrenal failure could not be excluded The hyperplastic thyroid generalized lymphadenopathy thymic hypertrophy and splenomegaly found at autopsy were consistent with a diagnosis of thyrotoxicosis Microscopic examination of the thyroid indicated toxic goiter Histologically it appeared more likely that the patient had toxic diffuse goiter with incidental nontoxic nodules than toxic nodular goiter in which the nodules were the source of the hyperthyroidism At autopsy a pituitary chromophobe adenoma was found which had destroyed all but about 5% of the normal tissue of the anterior lobe

Two possibilities are suggested to account for the association of the hyperthyroidism and pituitary adenoma (1) Hyperthyroidism may arise and be sustained in the presence of a sharply decreased mass and presumably functional activity of the anterior pituitary (2) Some chromophobe adenomas in man may be functional and may release enough thyrotrophin to produce hyperthyroidism

► [Werner has long been a proponent of the thyroidal origin of Graves disease and has used many indirect technics to answer the question Is Graves disease the result of excess pituitary stimulation I do not believe this particular publication contributes an answer since many patients with large pituitary tumors have no evidence whatsoever of loss of any pituitary function In addition, Gilliland found high levels of thyrotrophin in the serum of patients with Graves disease (Brit M J 1 378 Feb 18 19 6) Recently Dr Robert Bates at the National Institute of Health kindly applied his refined assay to the serum from 6 of our patients with Graves disease and found high levels of thyrotrophin —Fd]

(6) J Endocr L 18 76-2 0 M h 19 8

with clear cut Graves disease or obvious myxedema The problem arises in patients who have neither and who are never included in this type of study For these the physician may have to resort to a history and physical examination —Ed]

Use of Simple Thyroid Function Tests in Diagnosis of Hyperthyroidism is basically sound according to Ena K Bruck and I J L Goldberg (West London Hosp) who performed most if not all the following tests on each of 118 clinically euthyroid and 47 hyperthyroid patients BMR radioiodine thyroid clearance urinary radioiodine excretion (T index) trichloroacetic acid precipitable serum I^{131} at 48 hours after a tracer dose of protein bound iodine (PBI^{131}) serum PBI^{1} the radioactive iodine present in the thyroid gland 24 hours after a tracer dose (24 hour uptake) and the serum cholesterol

The author constructed a convention whereby the uppermost limit of each test (or lowermost for serum cholesterol) which would include 95% of the known euthyroid patients was used as a criterion of efficiency of that test in diagnosis of hyperthyroidism The proportion of the total number of hyperthyroid results for each test which fell outside the euthyroid range (as established by the convention) indicated the efficiency of a given test relative to the others

The thyroid clearance test was eliminated as being of essentially the same value as the T index but more *difficult* Choice of the other tests was based on their accuracy in diagnosis of hyperthyroidism Three tests—BMR T index and PBI^{131}—were chosen All were applied to 98 euthyroid and 44 hyperthyroid patients and the clinical diagnosis was confirmed by *at least one test in every case and by two tests in* all but 7

The T index assesses the rate of thyroid uptake of radioiodine the PBI^{131} gives information about the rate of release of thyroid hormone from the gland and the BMR is concerned with the tissue response to the hormone The efficacy of these tests is probably related to the facts that each examines a different aspect of thyroid metabolism and that there are no common sources of error to which all the tests are liable Singly they are no better than other established thyroid function tests but collectively they permit considerable diagnostic accuracy

(5) J Endocrin 18 77-28 February 1959

factors to be considered include racial and dietary differences e g the high carbohydrate content of the Japanese diet

The two diseases were much more likely to occur together in the male than in the female (20 5 1) In uncomplicated periodic paralysis the ratio is 3 1 A family history of periodic paralysis was noted in only 1 of the 119 patients in contrast to the high hereditary occurrence of uncomplicated periodic paralysis

Age of patients at onset of the paralytic attack was most often 20 39 whereas uncomplicated periodic paralysis usually develops in the first 2 decades of life especially during adolescence and onset later than the 3d decade is rare In most cases onset of attacks of periodic paralysis approximately coincided with or followed onset of hyperthyroidism The attacks of paralysis usually disappeared after effective treatment of hyperthyroidism

Attacks of periodic paralysis can be precipitated by ingestion of a large amount of carbohydrate and by injection of epinephrine As excessive amounts of thyroid hormone affect carbohydrate metabolism and increase the sensitivity of some tissues to epinephrine the thyroid hormone may precipitate attacks through these mechanisms

Relationship of Hyperthyroidism and Parkinsonism and the diagnostic and therapeutic problems posed by the possible concurrence of the disease are discussed by Elmer C Bartels and Rene R Rohart[9] (Lahey Clinic) A diencephalo pituitary pathologic process causing hyperthyroidism might presumably be precipitated by contiguity with a diencephalic lesion causing parkinsonism Symptoms common to both diseases are weight loss apparent or real loss of strength heat intolerance flushing of the skin with increased sweating emotional lability widened palpebral fissures stare tachycardia and tremor When the diseases coexist the symptoms of parkinsonism usually predominate so that identification of hyperthyroidism may be difficult Nevertheless such recognition is necessary since the patient with Parkinson s disease may deteriorate rapidly and die if the hyperthyroidism is not discerned Further in an elderly patient with parkinsonism plus an adenomatous goiter the

(9) A M A Arch Int Med 101 562 568 March 1958

Circulation in Hyperthyroidism Cardiac Catheterization Study before and after Treatment In hyperthyroidism the increased body metabolism imposes an extra load on the heart which may hypertrophy and in severe cases eventually fail Thyroid hormone may also cause abnormal cardiac rhythms with detrimental effect to the circulation Previous investigations have shown that the increased metabolic rate causes an increase in cardiac output Since the arteriovenous oxygen differences diminish the tissues apparently do not use more oxygen This is in contrast to the increased cardiac output accompanying exercise The stroke volume shows little change in thyrotoxicosis To elucidate further the effect of thyrotoxicosis on the circulation S Humerfelt O Muller and O Storstein[7] (Bergen Univ) performed cardiac catheterizations on 32 patients before and after treatment for thyrotoxicosis

The results confirmed previous impressions that increased cardiac output in hyperthyroidism is practically paralleled by increased heart rate Reduced cardiac output after treatment with antithyroid drugs is followed by a similar reduction in heart rate Changes in stroke volume and in arteriovenous oxygen differences are not significant However in patients with an extremely high cardiac output stroke volume may decrease after treatment The increased cardiac output in hyperthyroidism is accompanied by an elevation of the systolic pressure in the right ventricle and pulmonary artery with an increase in pulmonary artery pulse pressure Effective treatment reduces cardiac output systolic pressure and pulse pressure in the pulmonary and systemic circulations

► [The circulatory changes in hypothyroidism are described by Graettinger and co workers this YEAR BOOK p 45—Ed]

Association of Periodic Paralysis and Hyperthyroidism in Japan Shigeo Okinaka Kazuo Shizume Shiro Iino Akira Watanabe Minoru Irie Akito Noguchi Shizuo Kuma Kanji Kuma and Tadasu Ito[8] report that periodic paralysis was observed in 119 (1 9%) of 6 333 patients with hyperthyroidism operated on in 3 hospitals in Japan The association of the two disorders appears to be commoner in Japan than in Europe and the United States if one can judge from the number of reports in the literature The cause for this is not clear but

(7) Am Heart J 56 87 94 July 1958
(8) J Clin Endocr 17 1454 1459 December 1957

may produce an inconstant slight diminution in the value of certain thyroid parameters. P. M. Galletti, G. Jovet and O. Jallut (Univ. of Zurich) gave large doses of sodium fluoride over long periods to hyperthyroid patients on the hypothesis that a hyperfunctioning gland is more sensitive than healthy tissue.

Preliminary study of 15 patients with mild, moderate and severe hyperthyroidism after administration of 4-10 mg. sodium fluoride daily for 20-267 days showed delayed and inconsistent effects. A significant decrease in protein-bound iodine was observed in 9 patients, with a decrease in BMR in 7 and in initial fixation of radioactive iodine in 6. Definite clinical improvement, however, was observed in only 6 patients, of whom 3 showed decreased fixation of radioactive iodine.

Tests with radioactive fluorine showed no appreciable concentration of fluoride in the thyroid gland. The effects of fluoride are explained by inhibition of uptake of inorganic iodine by the thyroid, comparable to that of perchlorate but much less intense. This clinical study indicates that massive doses of sodium fluoride have no clinical value in hyperthyroidism.

Effect of Fluorine on Thyroidal Iodine Metabolism in Hyperthyroidism was studied by Pierre M. Galletti and Gustave Jovet[1] (Zurich) to elucidate the inhibitory effect of chronic administration of fluoride on thyroid function in the presence of hyperthyroidism, since the hyperfunctioning gland is a more sensitive structure than the normal gland. In 15 patients the BMR and protein-bound iodine (PBI) were determined before and after administration of 2-10 mg. fluoride ion (as sodium fluoride) daily over 20-245 days. In 10 patients the action of fluorine was checked by repeated radioiodine uptake tests in which the initial slope (T_0) of the uptake curve, which equals the uptake rate of inorganic plasma iodine, was taken as an indicator of the cumulative inhibiting action of fluorine.

In 6 patients the symptoms of hyperthyroidism were relieved and both the BMR and PBI concentration fell to normal levels. In the other 9, fluorine was clinically ineffective.

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(1) J. Cl. F docn 1 18 110 1110 Octobe 19 8

decision regarding surgical removal of the goiter may rest entirely on the presence or absence of hyperthyroidism

Certain features of hyperthyroidism are not part of the clinical picture of Parkinson s disease These include hyper orexia warm velvety smooth moist skin and thyrotoxic myopathy Moreover the tremor of parkinsonism is coarse and irregular nonintentional and of a resting type in con trast to the fine rhythmic tremor of hyperthyroidism

Radioactive iodine uptake serum protein bound iodine and BMR determinations may be of diagnostic value The au thors have found that evaluation of the BMR with anesthesia may often serve as a useful decisive diagnostic procedure Hyperthyroidism should be suspected in every case of par kinsonism It its presence is confirmed treatment of the hy perthyroidism will lead to improvement in coexi tent Par kinson s di ease

Antithyroid Drugs

Effect of Thiouracil on Serum and Liver Cholesterol of Athyreotic Rat was studied by Charles H Duncan and Maurice M Best[1] (Univ of Louisville) Thiouracil (0 5%) was added to the diet of athyreotic rats for 2 week and e rum and liver cholesterol concentrations were compared to those of athyreotic controls Thiouracil administration in creased the mean serum cholesterol and decreased the mean liver cholesterol Hepatic synthesis of cholesterol from C^{14} acetate was not significantly influenced by thiouracil

Thiouracil by altering the plasma liver partition of cho lesterol exerts a hypercholesterolemic effect that i inde pendent of its antithyroid action

► [This is a most important observation since many studies of the effect f reduced thyroid function including tho e on lipid metaboli m have been based on thiouracil induced hypothyroidism This study indicates that in the rat thiouracil increa e the serum cholesterol level in the al ence of thyroid Thus at least two mechanisms may be at work in the thiouracil treated intact rat (1) hypothyroidi m and (2) a direct effect on lipid partition —Ed]

Effects of Sodium Fluoride on Thyroid Function in Base dow s Disease Prolonged administration of small doses of fluoride (below 2 mg /day) does not change thyroid func tion significantly in normal man A larger dose however

(1) Am J Phy 1 194 351 354 A g t 1958

may produce an inconstant slight diminution in the value of certain thyroid parameters P M Galletti G Jovet and O Jillut (Univ of Zurich) gave large doses of sodium fluoride over long periods to hyperthyroid patients on the hypothesis that a hyperfunctioning gland is more sensitive than healthy tissue

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In 6 patients the symptoms of hyperthyroidism were relieved and both the BMR and PBI concentration fell to normal levels In the other 9 fluorine was clinically ineffective

(2) [illegible] 24 09 15 [illegible] 195[illegible]
(3) J Cl[illegible] E[illegible] 18 313 1110 [illegible] 1958

though an improvement in the BMR or PBI level was often observed The drop in the mean value for plasma PBI from 9 8 to 6 7 μg/100 ml and of the mean value for the BMR from +37 to +27% indicated definite inhibition of thyroid hyperfunction

In the radioiodine uptake studies an inhibitory effect of fluorine on the initial uptake was noted in 7 patients and in 4 of these the value of T_0 was reduced to the normal range by administration of fluorine over 67 245 days Though not as sensitive as the measurement of T_0 maximal uptake also decreased and thyroidal activity during the 1st week was modified A definite effect of fluorine usually appeared only after 40 50 days Interruption of fluorine intake in 2 patients with clinical and objective improvement was followed by relapse of hyperthyroidism and rise in the initial slope of radio iodine uptake

A minimal dosage of inorganic iodine (100 120 μg daily) was then given to 2 patients in whom initial uptake of radio iodine had been evidently lowered by fluoride therapy Both patients showed recurrence of hyperthyroidism and in 1 a goiter developed during fluoride therapy subsided during *iodine therapy and reappeared when the hyperthyroidism* was controlled by means of fluorine alone

No significant accumulation of radiofluorine in the thyroid was demonstrated in 2 patients so tested No inhibition of the rate of thyroidal iodine uptake was observed when excess fluoride was injected intravenously simultaneously with carrier free radioiodine Rather a slight increase of thyroidal uptake of inorganic iodine was noted

The conclusion is that fluorine inhibits the thyroidal iodide concentrating mechanism It does not impair the capacity of the gland to synthesize thyroid hormone when there is an abundance of iodine in the blood but when the total iodide pool is low inhibition of thyroidal concentrating capacity will impose a critical limitation of hormonal synthesis

Treatment of Eight Cases of Hyperthyroidism with Cobaltous Chloride is reported by Enrique Pimentel Malaussena Marcel Roche and Miguel Layrisse[4] (Central Univ Caracas) In 4 of the patients treated with varying dose of

(4) J A M A 167 1 19 17 A g 19 8

cobaltous chloride by mouth, clinical improvement was manifested by abatement of the tachycardia, reduction of BMR and rise in red blood cell count and in blood hemoglobin content. These 4 patients also gave striking evidence of improvement in laboratory tests with radioiodine, 3 of whom had thyroidectomy without complication after the cobalt therapy alone. One of the 4 had cobalt therapy for 117 days with apparent clinical remission.

A fifth patient who responded initially later escaped the effect of the drug and had to be given Lugol's solution before *operation*.

Three patients had no response to the drug; 1 of these did not respond to methimazole or potassium perchlorate and had to be given I^{131} therapy.

Exacerbation of Hyperthyroidism by Methimazole during Iodide Therapy was studied by Thaddeus E. Prout and Samuel P. Asper, Jr.[5] (Johns Hopkins Univ.) in 4 women treated for hyperthyroidism. One was started on potassium iodide 5 drops 3 times daily; 4 days later methimazole 15 mg. every 8 hours was given. The butanol extractable iodine (BEI) level and BMR gradually decreased throughout treatment without exacerbation of the hyperthyroidism. The second patient was given *potassium iodide 20 drops 3 times daily for* 21 days, whereupon the BEI level decreased from 12.6 to 2.7 μg./100 ml., with a concomitant decrease in BMR and improvement in symptoms. On the 21st day, iodide was stopped and methimazole 20 mg. every 8 hours started. During the next 7 days, the BEI and BMR *increased and symptoms of* nervousness and heat intolerance returned. Methimazole was continued and symptoms abated as the BEI and BMR returned to normal. A similar sequence was noted in the third patient. In the fourth, methimazole induced an exacerbation of hyperthyroidism despite continuance of iodide.

Release of thyroxin from the thyroid of patients with hyperthyroidism is stimulated by thyrotrophin and inhibited by iodide. Discharge of thyroxin from the thyroid can be stimulated despite iodide suppression, either by increasing the effect of the thyrotrophin or by decreasing the effect of the iodide. Iodide appears to block thyroxin release effectively in hyperthyroid patients, although thyroxin production

(5) A.M.A. Arch. Int. Med. 101:364-378, Feb., 1958.

continues In the patients studied methimazole induced release of thyroid hormone whether iodide was continued or not provided the iodide had been given sufficiently long The ensuing exacerbation was mild and transient and maximal 9 14 days after start of methimazole administration If thyrotrophin is given to patients with thyrotoxicosis under treatment with iodide the stimulation of the thyroid occurs within 24 hours suggesting that the release of thyrotrophin induced by methimazole in the present patients did not result from reactivation of inactive thyrotrophin already present The exact mechanism is unclear

Effect of Tetraethylthiuram Disulfide (Disulfiram Antabuse®) on Thyroid of Rat is similar in general to that of thiocyanate the radical of which it possesses Antti Telkka and Erkki Kivalo[6] (Univ of Helsinki) administered 25 mg/kg/day Antabuse® to rats weighing 200 Gm Other rats received 50 mg/kg/day potassium thiocyanate A third control group was untreated The mean final body weights of the rats when they were killed at 30 days showed that all animals had thrived However there was a statistically significant increase in thyroid weight relative to body weight in the rats treated with Antabuse® and a still greater increase in thiocyanate treated rats Histologic examination revealed that the thyroids in the control rats had a more flattened epithelium and a greater amount of colloid than those of both groups of treated rats No difference in the proportion of epithelium colloid and stroma was found between the Antabuse® and thiocyanate groups Presumably the common structural feature of the N C S group of thiocyanate and Antabuse is responsible for their antithyroid action

► [Before the advent of the current antihypertensive drugs thiocyanate was used to treat hypertension Some of the patients who received this agent developed goiters—a form of struma medicamentosa similar to the struma cibaria which Marine observed in rabbits fed large amounts of cabbage The combination of goiter and hypothyroidism should immediately make one think of iodine deficiency or ingestion of dietary or therapeutic goitrogens —Ed]

Antithyroid Activity of N Phthalyl Glutamic Acid Imide (K 17) This preparation which has the advantages of barbiturates without their undesirable side effects has been used in Germany as a sedative No data indicate whether the seda

(6) Act ... Soc ... 7 95 89 J ... y 1958

tive effect is a consequence of thyroid depression or of some other cause of hypometabolism

J McC Murdoch and G D Campbell[7] (Univ of Edinburgh) used the method of Stanley and Astwood to evaluate the effects of the compound on radioiodine uptake in 9 euthyroid patients Dosage ranged from 50-400 mg Results showed that N phthalyl glutamic acid imide has mild but definite antithyroid activity when given in doses of 200 mg or more The mode of action is unknown In doses of 200 mg or more the drug caused drowsiness in 5 patients

Use of the drug for long term sedation or hypnotic therapy is not justified pending results of a more detailed study of it long range effects in a larger series of patients notably those with hyperthyroidism

Radioiodine Therapy

Uptake of Iodine 131 by 18 Week Human Fetus D J Goldstein[8] (Johannesburg) administered 71 5 μc I^{131} to a woman 27 who had carcinoma of the thyroid with metastases An 18 week fetus was delivered by abdominal hysterotomy 6 days later and the fetal thyroid contained enough I^{131} to insure a radiation dose of at least 80 000 rad By autoradiography I^{131} was found in even immature follicles containing little or no colloid

Contrary to previous reports therapeutic I^{131} in the early stages of pregnancy is dangerous to the fetus A dose of 80 000 rad is far in excess of that which produces gross pathologic changes in an adult thyroid and it is extremely likely that the fetus if allowed to live would have had thyroid dysfunction and perhaps other pathologic changes Administration of therapeutic doses of I^{131} to women in this stage of pregnancy is unjustifiable unless one is prepared to terminate the pregnancy

Cataract Due to Tetany Following Radioactive Iodine Therapy is reported by Gilbert Dreyfus M Zara and Paule Gali[9]

Man 48 for 5 months had had symptoms of hyperthyroidism that had not responded to diiodotyrosine treatment Examination re

(7) B t M J 1 94 95 J 11 1958
(8) S th Af n M J 39 39 41 M 1 1958
(9) S ma n h p P 34 1301 1304 M 4 1959

vealed a firm goiter pulse rate of 100 BMR +29% and an I^{131} curve typical of hyperthyroidism (maximum of 70% at 6 hours 62% at 24 hours) He received 8 mc I^{131} (4 8 mc effective dose) which suppressed the symptoms Seven months later another dose of 8 mc was given because of exacerbation of hyperthyroid signs Ten months later the goiter had disappeared and hyperthyroidism was considered controlled Exophthalmos persisted and was not relieved by thyroxin or by depot corticotrophin X ray therapy was administered to the hypophysial region through 4 portals with a total surface dose of 6 000 r (depth dose about 2 000 r) Ocular protrusion which had been 25 25 receded to 22 22 5 but later increased at times to 25 26

Ten months after irradiation uncontrollable lacrimation and ocular irritation were accompanied by lowered visual acuity Bilateral cataracts were noted Vision in the right eye was 5/10 and in the left 4/10 protrusion 23 24 The levels of blood calcium had decreased to 5 5 mg /100 ml and of phosphorus increased to 5 mg /100 ml indicating parathyroid deficiency This was accompanied by involuntary contractures of the extremities some difficulty in swallowing and pharyngeal spasm Chvostek s sign was strongly positive The EEG showed no significant changes but an electromyogram seemed to show a tetanic doublet Months later after 45 injections of calcium gluconate intravenously the blood calcium level was still 6 4 mg /100 ml Later treatment with calcium was satisfactory with respect to general health and tetany

The authors review the 4 previously reported cases of parathyroid tetany following radioactive iodine treatment The present case appears to be the first in which a cataract developed Hence such complications are extremely rare and should not affect the established use of this type of therapy

► [This appears to be the first report of cataract associated with hypoparathyroidism following radioiodine therapy of Graves disease In none of the 5 cases of hypoparathyroidism in radioiodine treated patients is the cause and effect relationship between radioiodine and hypoparathyroidism established since pretreatment blood calcium levels were not reported In this case the cause of the cataract is likewise not clear since the patient had received x ray therapy to the pituitary 10 months earlier Jones pointed out the frequency of cataract following such therapy (Brit. J Radiol 24 637 1951) —Ed]

Thyroid Neoplasms Following Irradiation of the neck region are described by G M Wilson R Kilpatrick H Eckert R C Curran R P Jepson G W Plomfield and H Miller[1] (Univ of Sheffield)

Six patients were irradiated in infancy or childhood for treatment of nevi keloids or eczema The estimated maximum dose to the thyroid ranged from 130 to 2 700 r and some patients received two courses of therapy Radiation sources

(1) B r M J 2 9 9934 Oct 18 1958

were x rays or radium The children were aged 2 months to 16 years when radiation was administered 5-18 years intervened before the first sign of a goiter In each instance the malignant tumor was a papillary carcinoma in 1 a combination of papillary and follicular types One tumor was associated with hyperthyroidism Treatment of the malignant tumors was by surgery when possible followed in some cases by radiotherapy In some of the younger patients thyroxin was given postoperatively to suppress the pituitary as there is some evidence that diminution of thyrotrophin may check the growth of some thyroid carcinomas All patients in this group were alive and free from recurrence when last seen at periods of less than 1 to over 9 years after excision of the carcinomas despite the demonstration of metastases at surgery to adjacent or nearby nodes in several cases

A seventh patient was given repeated x ray therapy for thyrotoxicosis during 1918 22 No details of dosage were available but from the residual skin reaction it is probable that more than 2 000 r were given About 33 years after the last x ray therapy a goiter was observed which was excised some months later Histologically there was an undifferentiated anaplastic carcinoma with pleomorphism and numerous mitoses One month after surgery the tumor recurred and x ray therapy was given Death occurred 6 months later following continued enlargement of the tumor

In 2 patients an adenomatous enlargement of the thyroid was discovered many years after irradiation In 1 irradiation of a nevus during infancy was followed by development of an adenomatous neoplastic tumor The other patient was given a dose probably in excess of 2 000 r for thyrotoxicosis Twenty years later an adenoma was excised which was hyperplastic but not definitely carcinomatous

It is believed that exposure to ionizing radiation in childhood predisposes to the appearance of thyroid neoplasms whereas the association in adult life is less certain

► [The frequency of a history of previous radiation in youngsters with thyroid carcinoma seems to increase in proportion to the thoroughness with which it is sought In a recent publication Petit Catz and Starr obtained such a history in 9 of 11 patients under age 20 (California Med 89 394 1958) —Ed]

Acute Leukemia after Radioactive Iodine I^{131} Therapy for Hyperthyroidism was reported by Sidney C Werner and

vealed a firm goiter pulse rate of 100 BMR +29% and an I^{131} curve typical of hyperthyroidism (maximum of 70% at 6 hours 62% at 24 hours) He received 8 mc I^{131} (4 8 mc effective dose) which suppressed the symptoms Seven months later another dose of 8 mc was given because of exacerbation of hyperthyroid signs Ten months later the goiter had disappeared and hyperthyroidism was considered controlled Exophthalmos persisted and was not relieved by thyroxin or by depot corticotrophin X ray therapy was administered to the hypophysial region through 4 portals with a total surface dose of 6 000 r (depth dose about 2 000 r) Ocular protrusion which had been 25 25 receded to 22 22 5 but later increased at times to 25 26

Ten months after irradiation uncontrollable lacrimation and ocular irritation were accompanied by lowered visual acuity Bilateral cataracts were noted Vision in the right eye was 5/10 and in the left 4/10 protrusion 23 24 The levels of blood calcium had decreased to 5 5 mg /100 ml and of phosphorus increased to 5 mg /100 ml indicating parathyroid deficiency This was accompanied by involuntary contractures of the extremities some difficulty in swallowing and pharyngeal spasm Chvostek s sign was strongly positive The EEG showed no significant changes but an electromyogram seemed to show a tetanic doublet Months later after 45 injections of calcium gluconate intravenously the blood calcium level was still 6 4 mg /100 ml Later treatment with calcium was satisfactory with respect to general health and tetany

The authors review the 4 previously reported cases of parathyroid tetany following radioactive iodine treatment The present case appears to be the first in which a cataract developed Hence such complications are extremely rare and should not affect the established use of this type of therapy

► [This appears to be the first report of cataract associated with hypoparathyroidism following radioiodine therapy of Graves di ease In none of the 5 cases of hypoparathyroidism in radioiodine treated patients is the cause and effect relationship between radioiodine and hypoparathyroidism established since pretreatment blood calcium levels were not reported. In this case the cause of the cataract is likewise not clear since the patient had received x ray therapy to the pituitary 10 months earlier Jones pointed out the frequency of cataract following such therapy (Brit J Radiol 24 637 1951) —Ed]

Thyroid Neoplasms Following Irradiation of the neck region are described by G M Wilson R Kilpatrick H Eckert R C Curran R P Jepson G W Blomfield and H Miller[1] (Univ of Sheffield)

Six patients were irradiated in infancy or childhood for treatment of nevi keloids or eczema The estimated maximum dose to the thyroid ranged from 130 to 2 700 r and some patients received two cour es of therapy Radiation sources

(1) B t M J 2 9 934 O t 18 1958

total 16 cases documented 12 have been in women aged 57 88 11 had involvement of both eyes 5 of only one There was no correlation with the severity of hyperophthalmopathy At no time did any patient show visual loss beyond the ability to count fingers The visual decrease occurred fairly rapidly over 2 6 week In 14 patients visual loss tended to reach a climax then abate In 2 visual acuity in at least one eye remained poor because of onset of optic atrophy The course seemed independent of the treatments attempted

Visual field defects were fairly consistent with central or paracentral scotoma a defect of a nerve fiber bundle or a combination of the two Most patients showed the central scotoma type of defect the scotoma possessing sharp borders with a density varying from 1/1 000 up to and including 35/1 000 white test objects and varying from 5 to 30 degrees in diameter Ophthalmoscopic examination consistently showed no cause for the visual loss Possibly the lesion is produced not by mechanical or toxic factors acting directly on the nerve fibers but by factor affecting the optic nerve indirectly through its vascular supply

Neither the clinical status of the thyroid at onset of the disorder nor the usual treatments prescribed for the basic thyroid pituitary dysfunction seem to have any influence on the course of the optic neuropathy Prognosis is good in most patients with return of useful vision Vision improves without orbital decompression Loss of vision due to this disorder of the optic nerves need not be considered an indication for decompression However for patients with Graves disease and papilledema orbital decompression should be seriously considered as the treatment of choice

Gross Digital Clubbing and Exophthalmic Ophthalmoplegia in Thyroid Disorders The role of the pituitary gland in the production of exophthalmic ophthalmoplegia and in the pathogenesis of digital clubbing has been studied and reviewed by many workers The concept of an exophthalmos producing hormone as a separate entity from the thyroid stimulating hormone of the pituitary gland is now widely held In the light of clinical and autopsy findings the development of acropachy and chronic hypertrophic pulmonary osteoarthropathy in some patients with bronchogenic carci

Edith H Quimby (Columbia Univ) in woman 28 with toxic recurrent goiter despite thyroidectomy who was given a total of 21 mc I^{131} for diagnosis and therapy over 4 months After an absence of 14 months she returned with acute leukemia probably granulocytic

Five cases of acute leukemia have appeared after treatment of hyperthyroidism with I^{131} an incidence of 1/13000/year The spontaneous incidence of acute leukemia has been estimated to be 1/20000 persons/year Some have estimated that the spontaneous rate is doubled by general body exposure i e by exposure of the whole red marrow of the body to 30 50 r This is considerably above the calculated general body exposure during treatment for hyperthyroidism which in this case was between 1 and 3 rad

The authors conclude that the association of leukemia and I^{131} therapy for hyperthyroidism probably is no more than chance However the postulation that the leukemogenic effect of radiation is proportional to dose may pertain here so that the incidence of leukemia with 5 r exposure e g would be increased by 10% Although the mechanisms by which the relatively low radiation exposures provided by I^{131} therapy in hyperthyroidism might induce leukemia are not evident it is important that all occurrences of leukemia in patients receiving such therapy be recorded in detail to establish whether the association of the disease and the radioactive I^{131} treatment is more than coincidental

EXOPHTHALMOS

Optic Neuropathy of Exophthalmic Goiter (Graves Disease) Patients with exophthalmic goiter may complain of blurred vision In most this is due to a change in refraction resulting from increased pressure in the orbits and in some to change in the cornea secondary to exposure or to glaucoma John W Henderson[3] (Mayo Clinic and Found) reports 6 cases in which the visual disorder was in the optic nerve This is an infrequent cause of visual disturbance and is seldom recognized

There may be no papilledema or any other visible manifestation of ocular dysfunction except loss of vision Of the

( ) J A M A 165 1558 1559 No 3 195
(3) A M A Arch Ophth 59 471 490 Ap 1 1958



Fig. 13. Clubbing of fingers. (Courtesy of Drs. Danforth, W. H., and Humphrey, H. A., J. Clin. Endocrinol. 18:130, 1307, November 1958.)

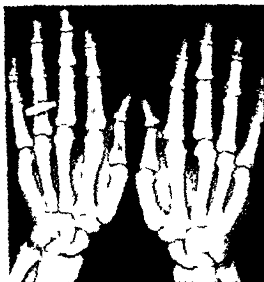


Fig. 14.—Hypertrophic osteoarthropathy. (Courtesy of Drs. Danforth, W. H., and Humphrey, H. A., J. Clin. Endocrinol. 18:130, 1307, November 1958.)

Radiographs of the entire body revealed periosteal proliferations characteristic of hypertrophic osteoarthropathy involving all metacarpals and proximal phalanges of the hand and the 5th metatarsals (Fig. 14). A few minute periosteal proliferations in several middle phalanges of the hand were presumably similar in nature and etiolo

noma has been ascribed to a disturbance of pituitary function

A G Freeman[4] (Univ of Bristol) reports autopsy findings in *2 patients with medically induced or postoperative hypothyroidism* associated with malignant exophthalmos pretibial myxedema and gross digital clubbing One patient had an eosinophilic chromophilic adenoma of the pituitary gland and 1 had eosinophilic hyperplasia of the anterior lobe of the pituitary gland Neither patient had a history or clinical evidence of pulmonary cardiac hepatic or intestinal disease and no family history of clubbing of the fingers

The association of acropachy and exophthalmic ophthalmoplegia in patients with postoperative or medically induced myxedema is not as rare as might be expected from the paucity of published reports The development of severe digital clubbing and exophthalmic ophthalmoplegia in untreated active thyrotoxicosis however as occurred in 1 of the patients a man aged 54 does not appear to have been previously described

The fact that gross digital clubbing is now reported in association with exophthalmic ophthalmoplegia in hyperthyroid as well as in induced euthyroid and hypothyroid states adds further support to the view that this syndrome with or without pretibial myxedema is a clinical manifestation of pituitary dysfunction

Hypertrophic Osteoarthropathy and Pretibial Myxedema *Associated with Graves Disease* were observed by William H Danforth and Harvey A Humphrey[5] (Washington Univ) Both manifestations followed an induced remission of Graves disease

Man 46 was hospitalized for swelling of lower portion of legs The entire skin circumference of each leg from just below the knee to the ankle was conspicuously thickened and indurated Raised irregular nodular areas were noted Hair follicles were prominent and individual hairs coarse and short The skin was darker than normal Pitting edema (2+) was noted over the dorsal surface of each foot Microscopic sections from the biopsy specimen of the thickened skin showed large amounts of mucicarmine positive material between separated collagen fibers The specimen was typical of pretibial myxedema The fingers were clubbed (Fig 13) and the toes were questionably clubbed Definite bony prominences were palpable over the dorsum of each 5th metacarpal

(4) La t 57-60 J ly 1? 1958
(5) J Cl n E doc nol 18 130 1307 No mber 1958

Exophthalmos and Localized Pretibial Myxedema in Euthyroid Patient Studies with Triiodothyronine Monte A Greer[7] (Univ of Oregon) studied the effect of triiodothyronine on the thyroid secretion rate of I^{131} in a woman with exophthalmos and localized myxedema without hyperthyroidism The rate was much faster than that of other euthyroid patients and faster than the average for most thyrotoxic patients It was not significantly suppressed by oral administration of up to 400 µg triiodothyronine daily though this large dose produced toxic symptoms

The cause of the abnormal thyroid activity in this patient is not apparent Turnover in the thyroid must have been extremely fast The dramatic fall in the level of serum protein bound iodine was much faster than any seen even in thyrotoxic patients and considered with the rapid secretion rate it suggests a small pool of hormonal iodine in the thyroid Clinical thyrotoxicosis will probably develop in this patient eventually but at present (more than 12 months after initial admission) she is euthyroid

Studies of the penetration of labeled triiodothyronine into the normal skin and skin of the localized myxedematous area showed no significant difference between the concentrations in the two tissues The results indicate that whatever the cause of the localized myxedema it is not related to a relative failure of triiodothyronine to enter the skin tissues

THYROID CANCER

Persistent Thyroid Carcinoma A characteristic of some thyroid cancers is slow rate of growth Although such tumors often can be held in check or temporarily cured by various forms of treatment persistence with recurrent symptoms after 5 or more years is relatively common hence follow up for 10 and even 20 years is necessary to evaluate thyroid carcinoma adequately William A Meissner and Merle A Legg[8] (New England Deaconess Hosp) report 17 cases (15 females) in which thyroid carcinoma persisted 10 26 years Age at time of original treatment was 8 56 years 10 were under 37 and 7 were 53 56 The tumor had been present 10 14 years in 9 and 17 years or over in 8

(7) J Clin E doc 1 17 1466 34 1 D mb 1357
(8) Ibid 18 91 98 J ary 1958

gy The mo t minute deviation from normal appearance was a localized excrescence projecting outward from the diaphysial cortex the most advanced proliferations extended the length of the diaphysis but spared the epiphysial region including the articular cortices Discrete isolated rarefactions in several of the proliferations of the phalange were considered to represent preosseous tissue The cortice of the tibia fibula and ulna appeared thick but not definitely pathologic Exophthalmo of the right eye was al o noted

Though hypertrophic osteoarthropathy can occur during the course of Graves disease in 7 cases reviewed it became evident after induced remission of the hyperthyroid manifestations of the disease It is usually or perhaps invariably associated with pretibial myxedema Like the ophthalmopathy and pretibial myxedema the osteoarthropathy does not seem to depend on the hyperthyroid a pects of Grave disease

Function of Thyroid in Euthyroid Patients with Exophthalmos The BMR protein bound iodine (PPI) level and radioiodine uptake may be normal low or high in the presence of severe exophthalmos To study further thyroid function in this di order Thorkild Friis and Earle M Chapman[6] (Harvard Med School) measured the BMR PPI thyroid uptake of I^{131} and conversion to serum PBI^{131} and analyzed paper chromatograms of the serum after oral radioiodine in 8 clinically euthyroid patients with exophthalmos

The BMR 24 hour radioiodine uptake and PBI were normal in 4 the BMR slightly increased in 1 the PBI low in 1 and increased in 1 and the radioiodine uptake above normal in 1 The conversion ratio was increased (over 50%) in all and the PBI^{131} was elevated in half the patient In the controls euthyroid patients without exophthalmo conversion ratios were under 40% in none was the PBI^{131} elevated Paper chromatography revealed radioactive iodide and thyroxin in the serums of all 8 patients with exophthalmos Radioactive triiodothyronine wa demonstrated in only 3 patients and appeared later than thyroxin

The re ults indicate that the thyroid tissue in patients with exophthalmos is overactive and producing a normal amount of hormone and suggest that storage of iodinated substances in the gland is lowered Usually normally iodinated thyronines are secreted

(6) A t endoc 1 27 07 15 Febru ry 1959

dicted on the basis of histology Every major type of thyroid cancer was observed including undifferentiated giant cell usually considered the most malignant of all thyroid tumors Persistent thyroid cancer is not limited to young persons

► [It is noteworthy that not all of these slow growing carcinomas are of the papillary variety The only thyroid carcinoma with a uniformly rapid lethal effect is the anaplastic or small cell variety Since however one cannot be certain of the course until it is examined retrospectively every thyroid carcinoma should be treated aggressively Even papillary adenocarcinoma can kill rapidly —Ed]

Use of l Triiodothyronine as Pituitary Depressant in Management of Thyroid Cancer according to Colin G Thomas Jr[9] (Univ of North Carolina) offers advantages over other methods Adequate suppression may be deduced from measurements of the serum protein bound iodine (PBI) because endogenous thyroxin is firmly associated with a specific alpha globulin but binding of l triiodothyronine is not firm

After the type extent and functional activity of the neoplasm in 10 patients were studied serum (PBI) levels and radioiodine uptake were determined l Triiodothyronine was given by mouth beginning with 25 µg twice daily then the dose was increased at 1 2 week intervals until the tolerated maximum or a level of 200 300 µg daily was reached This dosage was continued for 6 52 weeks or more Periodic determinations of serum PBI showed that endogenous hormone was reduced to the hypothyroid range within 6 weeks leveling off at an irreducible minimum beyond which increased dosage and prolonged administration produced no effect It was probable that this represented complete suppression of the pituitary effect The dosage required was variable as little as 50 µg daily in some

In 1 patient whose metastases showed autonomy of growth a level below two could not be reached In 2 patients with total thyroidectomy functioning pulmonary metastases showed decreased output of iodinated protein after start of therapy and in 1 patient showed decrease in size of the metastases Tolerance varied some showed symptoms of hyperthyroidism at 100 150 µg daily and others tolerated 200 350 µg without symptoms The action of the drug persisted several days after cessation of therapy

Radioiodine uptake was accomplished in all patients with

(9) Surg Gyn & Obst. 106 13 144 Feb ay 1958

The table shows the original and final types of tumor Initial treatment included excision, irradiation and radical neck dissection Six patients had local excision only 8 had local excision followed by irradiation and 3 had radical neck dissection plus irradiation None of the 17 patients had what

Original and Final Type of Tumor in 17 Cases of Persistent Thyroid Carcinoma

Patient			Original tumor type	Years persistent	Final tumor type
No.	Age at time of first treatment (yrs)	Sex			
1		F	Follicular	10	Follicular
	4	M	Undifferentiated (giant-cell)	10	Undifferentiated (giant-cell)
3	36	F	Follicular	11	Follicular
4	3	F	Follicular	12	Follicular
5		F	Papillary	1	Papillary
6		F	Undifferentiated	1	Undifferentiated
7	5	F	Undifferentiated	13	Undifferentiated
8	[illegible]	[illegible]	Follicular	13	Undifferentiated (giant-cell)
9	3	M	Follicular	14	Follicular
10	[illegible]	F	Follicular	17	Follicular
11		F	Papillary	1	Papillary
1	4	[illegible]	Follicular	0	Follicular
13	36	[illegible]	Papillary	20	Papillary
14		[illegible]	Mixed papillary and follicular	[illegible]	Mixed papillary and follicular
1	21	[illegible]	Follicular	[illegible]	Follicular
16	31	F	Mixed papillary and follicular	4	Mixed papillary and follicular
17	11	F	Papillary	6	Papillary

would be considered vigorous or even adequate initial surgery Six received desiccated thyroid after surgical therapy

Persistent tumor was limited to the neck in 9 6 had no recurrence in the neck Two had tumor in the neck and in distant sites Six had metastasis to the lung 4 to bone 1 to the brain and 2 to more than one viscus Of the 7 deaths 5 were attributed to thyroid cancer 2 from local extension 2 from disseminated metastases and 1 from metastasis to the brain

Prolonged persistence of thyroid cancer cannot be pre-

Extraction and Estimation of Human Urinary Parathyroid Hormone using a benzoic acid adsorption method of extraction is reported by Beryl M. A. Davies[1] (Postgrad Med School London)

METHOD—A 48 hour specimen of refrigerated urine was acidified with hydrochloric acid to pH 3.5. Saturated benzoic acid in dilute ethanol was added and the precipitated benzoic acid adsorbed the parathyroid hormone. The precipitate was dried and washed in dilute ethanol which dissolved the benzoic acid but left the precipitate containing parathyroid hormone. Bioassay of parathyroid hormone was accomplished using a previously described method based on the increase in urinary phosphate excretion after injection of parathyroid hormone into normal mice

No substances have been found which increase the excretion of urinary phosphate in mice under the conditions of the assay except parathyroid hormone. Benzoic acid had no effect on the urinary phosphate excretion nor did it prevent response to injected commercial Para thor mone*

Human urinary extracts were assayed against Para thor mone* Para thor mone was assigned 100 phosphate units/ml the mean value for normal human urinary excretion of parathyroid hormone was 60.4 (range 47-72) phosphate units/24 hours. In 4 subjects with confirmed hyperparathyroidism and concurrent uremia the mean was 121.2 (range 103-146) phosphate units/24 hours. Four subjects with hypoparathyroidism had amounts too small to be assayed (less than 30 phosphate units/24 hours)

The benzoic acid method and mouse assay are valid procedures for extraction and quantitation of parathyroid hormone in human urine

Ultrafiltrable Calcium of Human Serum II Variations in Disease States and under Experimental Conditions The total serum calcium is composed of two major fractions nondiffusible or protein bound calcium and diffusible or ultrafiltrable calcium. The diffusible portion is predominantly ionic calcium. It theoretically traverses capillary membranes in vivo and participates in metabolic processes at the cellular level. In normal adults 60-70% of serum calcium is ultrafiltrable

A Raymond Terepka T. N. Toribara and Priscilla A Dewey (Univ of Rochester) determined the ultrafiltrable

(1) J. Endocrinol. 16:3?9 3 ... Sep 1 ... 8
( ) J Cl ... In ... 37 8 98 3 ... 1

functioning carcinoma There was no autonomy of iodine uptake as in Graves disease When thyroidectomy was possible the morphology of normal and neoplastic gland tissue was studied After 1 year involution and atrophy was apparent in the normal gland and to lesser degree in the neoplastic The neoplastic gland remained more columnar and showed no colloid production Uptake of P³ in normal hyperplastic carcinomatous and treated glands was studied The increased uptake in cancerous tissue approximated that of the hyperplastic gland When normal and cancerous thyroid tissue coexisted the uptake was more readily suppressed in the normal tissue than in the neoplasm

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THE PARATHYROID GLANDS CALCIUM METABOLISM AND METABOLIC BONE DISEASES

► Despite the fact that the diagnosis of hyperparathyroidism depends on indirect measurement of the effects of excess parathyroid hormone rather than on direct measurement of the hormone the frequency with which this disease is being detected is increasing by leaps and bounds Black has pointed out (Am J Surg 96 613 1958) that the nonspecific symptoms of hyperparathyroidism uncomplicated by renal or osseous disease make it difficult for the clinician to know which patients should be subjected to chemical diagnostic technics It is gratifying to read an editorial by an experienced surgeon which clarifies the crucial point that the diagnosis must be established chemically This philosophy reduces the number of explorations for parathyroid tumor Black s editorial further points out that the clinician is at the mercy of the laboratory and that it therefore must be capable of making accurate measurements of serum calcium—by no means a simple feat Thus as Black says Case finding remains notably unsuccessful except in clinics in which a special interest in hyperparathyroidism on the part of urologists internists and clinical pathologists has developed The workings of such special interest is changing our concept of the clinical symptoms of hyperparathyroidism from bone to stone to abdominal moan to none at all! In our experience clinical suspicion followed by a reliable demonstration of hypercalcemia and pinning down the differential diagnosis of hypercalcemia has resulted in the recognition of 66 cases in 4 years It is hoped that direct assay of parathyroid hormone as described in the subsequent article by Beryl Davies will further our knowledge and diagnostic accuracy Hypercalcemia from other causes has usually been considered uncommon but it is now clear that it is a relatively common chemical finding in patients with advanced breast cancer thyrotoxicosis sarcoidosis and miscellaneous malignancies with or without osseous metastases when reliable measurements of serum calcium are used —E I

renal di ea e a high percentage of ultrafiltrable calcium is almo t invariable regardless of the level of serum proteins so that the actual quantity of ultrafiltrable calcium ap proaches normal The amount of calcium bound to serum proteins appears to be specifically altered This accounts for the clinical observations that tetany is infrequent in renal disease

Abnormalities in concentration of ultrafiltrable calcium indicate disturbances in the bone extracellular fluid calcium equilibrium abnormalities in percentage of ultrafiltrable cal cium (ratio of ultrafiltrable to total serum calcium) are related to altered calcium protein interrelations in serum

► [Using a different technic we too have found that the percentage of nonprotein bound calcium is not altered in hyperparathyroidism so that the observed increase of nonprotein bound calcium merely reflects the in creased total calcium level In this respect we are distinctly at odds with Lloyd and Rose (Lancet 2 1258 Dec 13 19 8) who believe that the demonstration of an increa e in the level of ionized calcium in the serum is important in the diagnosis of hyperparathyroi li m In my opinion failure to demonstrate increased total calcium levels in such cases probably repre sents laboratory error since we have now seen a number of ca es of hyper parathyroidism with hypercalcemia in our laboratory despite normal values simultaneously reported from many other laboratories At the present writing I believe it accurate to say that the keystone of diagnosis depends on a reliable demonstration of hypercalcemia —Ed.]

Radiocalcium Studies of Bone Formation Rate in Human Metabolic Bone Disease Calcium[4] tracer studies were per formed in 11 adults with bone disease and 1 normal man aged 65 by Robert P Heaney and G Donald Whedon[3] (Nat l Inst of Health) The size of the miscible calcium pool aver aged slightly less than 100 mg calcium/kg in all except 2 patients with osteitis deformans in whom the pools were four times that size A direct relation between the size of the pool and the rate of bone formation was attributed to the variable contribution of the mass of newly formed bone to the miscible calcium pool

Evidence indicates that this pool despite its theoretical complexity behaves as a single compartment The turnover of this pool is greatly in excess of combined excretory loss and is therefore presumed to include loss of tracer into non exchanging bone in the process of bone formation

On the basis of a study in 1 normal adult in the present series and of available studies in the literature the normal

(3) J Cl E Inc 1 18 1 46-1 67 N be 19

ity of serum calcium in persons with hyper and hypocalcemia before during and after parenteral administration of calcium citrate phosphate and parathyroid extract

The distribution of calcium in serum between ultrafiltrable and nonultrafiltrable forms is governed by a purely physical chemical process the mass action relationship $Ca^{++} + \text{Protein} \rightleftharpoons \text{CaProteinate}$ in hypercalcemia whether secondary to a disease or experimentally induced by administration of calcium or parathyroid extract Calcium added to serum in vivo increases the ultrafiltrate calcium and proportionately increases the protein bound calcium so the ratio remains constant The same relation is clearly demonstrated in vitro

The parathyroids are concerned with equilibrium between calcium in bone and extracellular fluid Once in the serum the calcium released from bone obeys the law of mass action in its reaction with serum proteins Hypoproteinemia with presumably normal parathyroid function is associated with a low total serum calcium a normal or near normal concentration and a high percentage of ultrafiltrable calcium The concentration of calcium in ultrafiltrates of serum is determined by the bone extracellular fluid calcium equilibrium whereas the total serum calcium and consequently the percentage of ultrafiltrable calcium is secondarily determined by mass law relationships in serum or plasma Total calcium in serum reflects the level necessary to maintain the concentration of ultrafiltrable or ionized calcium determined by the parathyroid controlled bone extracellular fluid equilibrium and serum mass law relation

The hypercalcemia of malignant disease Boeck s sarcoid and vitamin D intoxication is associated with elevated concentrations of ultrafiltrable calcium whereas the percentage of the total which is ultrafiltrable is within the range for normal persons with normal serum proteins These findings indicate that the calcium disturbance is also due to a primary alteration in the bone extracellular fluid calcium equilibrium with secondary changes in total serum calcium

Hypocalcemia is accompanied by a normal or high percentage of ultrafiltrable calcium When the percentage is normal the serum proteins are usually normal When the percentage is high the serum proteins are usually low In

inhibit the effects produced by 90 μg pellets of estradiol benzoate placed subcutaneously However the androgen inhibited estrogenic activity not only in the drilled femur but also in the contralateral one

No sexual differences were observed in response to the dosage of hormones given Differences in femoral changes between castrated and noncastrated mice were not seen

The Hypocalcemias

So-called Pseudohypoparathyroidism and Neurogenic Tetanies H P Klotz and I Kahn[5] found in 2 sisters aged 14 and 18 the following manifestations which were more severe in the younger (1) definite tetany clinical electric and biologic hypocalcemia (2) structural anomalies i e small size rounded head and plumpness (3) cerebral disturbances accompanied by clinical epilepsy in the younger girl with definite EEG changes in the other both showed striking mental retardation In view of these findings these cases should be classified as pseudoparathyroidism

Investigation of the family history showed that the father was normal The mother was short round faced and obese but displayed no clinical signs of tetany Of 9 infants born to the mother including the 2 patients 3 died at an early age of bronchopneumonia during an epidemic of measles 1 died at age 10 of meningitis (she had had epileptic seizures dating from infancy and severe mental retardation) and 1 daughter 24 was normal These 5 were offspring of a first marriage (the first husband died accidentally) From the second marriage there were 4 children the 2 patients a son dead at birth (weight 11 lb) and a daughter 7½ with extreme nervousness and clinical signs of tetany (Chvostek sign +++) An effort is being made to determine whether this tetany is similar to that in the 2 patients although the 7½ year old girl does not have their habitus nor mental retardation

This family history furnishes an argument for classifying the 2 sisters in the same category especially since 8 of 40 reported cases of pseudohypoparathyroidism were familial In Albright s nomenclature diagnosis in the younger sister would be pseudohypoparathyroidism because of definite

(5) S ma h p P 33 377 1 0 N 10 19

rate of bone formation is estimated to be about 9 mg calcium/kg/day (mean for 10 subjects 9 1±0 9 S D) The rate of bone formation in 6 patients with osteoporosis without parathyroid disease was 9 4±1 07 A much reduced rate of bone formation was found in 1 patient with uncomplicated hypoparathyroidism a slightly elevated rate in a young man with familial hyperostosis and greatly elevated rates in 2 patients with osteitis deformans

From the time of return of bone isotope into the pool the biologic life of the shortest lived species of bone was estimated and measurement was made of the proportion of total bone formation represented by this recycling In general the time required for this earliest recycling seemed to vary inversely with the postulated turnover of bone

► [Since the patients weights are not included in the report the data cannot be satisfactorily converted to total rates of bone formation If we assume that the osteoporotic subjects averaged 70 kg in weight, the rates given in this study are identical with those we have reported using non radioactive strontium as a tracer Whether weight is as important as suggested seems uncertain It does not seem reasonable that a 300 pounder who loses 100 lb by dieting thereby reduces his skeletal mass by one third In our studies no such relation is apparent the rate of osteogenesis in 24 patients with senile osteoporosis was 33 mEq (660 mg) calcium/day whereas that of 22 normal subjects of the same age and weight was 47 mEq /day (940 mg)—a statistically significant difference —Ed]

Inhibition of Estradiol Induced Endosteal Bone Formation after Intrafemoral Implantation of Testosterone Propionate into Mice is reported by Howard K Suzuki[4] (Yale Univ) Cavities were drilled in the right femora of 167 mice and pellets of hormones or placebos were placed in these cavities

Mice that only had cavities drilled or that had cholesterol placebos or testosterone propionate pellets implanted intrafemorally showed little endosteal bone proliferation in the distal metaphyses and callus formation at the drilled sites 4 weeks after implantation Both intrafemoral and systemic applications of 90 μg estradiol benzoate induced localized hyperostosis in the traumatized regions However 4 weeks after hormone implantation the distal metaphyses of both femora showed about equal endosteal proliferation due to the systemic effects of estradiol benzoate Over 80 μg testosterone propionate placed intrafemorally was needed to

(4) J B & J t S g 40 A 43 445 Ap 1 1958

phaturia was demonstrated after intravenous administration of parathormone[*] (Ellsworth Howard test) A normal control was not run however and it was considered that without a concurrent control this was not necessarily a significant determination There was no abnormal bone density metacarpal shortening or metastatic calcification An intravenous calcium tolerance test was followed by increase in urinary phosphorus when the serum calcium was elevated in direct contrast to the response expected in normal person

Clinical improvement occurred in this patient before correction of the hypocalcemia Improvement coincided with a decreasing serum phosphorus level however suggesting that hyperphosphatemia together with hypocalcemia may be important in the production of neurologic manifestations in this disease There may be a closer relation of the central nervous system manifestations of hypoparathyroidism to hyperphosphatemia than has been previously appreciated The relation to hypocalcemia alone appears inexact and in particular psychoses are absent in patients who are hypocalcemic as a result of vitamin D deficiency The concurrent liver disease may have aggravated the parathyroid insufficiency by impairing absorption of vitamin D and it may have played a role in the delayed response to treatment

Hypocalcemic Hypercalciuria during Vitamin D and Dihydrotachysterol Therapy of Hypoparathyroidism in 10 patients suggested to Jorge Litvak Marc P Moldawer Anne P Forbes and Philip H Henneman[7] (Harvard Med School) a direct renal effect of these compounds Urinary calcium ordinarily varies with the level of serum calcium Patients with hypoparathyroidism characteristically present hypocalcemia and hypocalciuria before treatment but during treatment calcium excretion may be excessive despite low levels of fasting serum calcium Before therapy the expected hypocalcemia and hypocalciuria were present in the patient studied Vitamin D given alone dihydrotachysterol given alone or both given simultaneously resulted in hypercalciuria although serum levels of calcium remained low There was no obvious relation between serum phosphorus level and urinary calcium

Vitamin D and dihydrotachysterol raised the serum calcium level toward normal by increasing absorption of calcium from the gastrointestinal tract and by increasing bone

(7) J Cl E loc 1 18 46 M h 1 58

humoral signs In the other it would be pseudopseudohypo parathyroidism showing that this terminology is not ideal Respecting the value of Albright s clinical descriptions the authors propose reclassification into a single entity called multidystrophic tetany of Albright This should be defined as a genetic affection with several clinical masks ranging from predominant dystrophies manifesting pseudopseudo hypoparathyroidism to those cases in which a central nervous disturbance is pre eminent producing a neurogenic tetany in which a minor dystrophic element or familial occurrence points to the genetic character Between these two extremes multiple clinical forms can be distinguished which have been described as pseudohypoparathyroidism and which are far from monomorphic

New methods of determining titers and constants in para thyroid activity may reveal whether the renal tubule pos sesses the nonreceptivity to parathyroid hormone which Al bright has described but this seems to await final proof Investigations should also aim to discover whether this non receptivity is congenital or results from an excess or chronic lack of hormone In any case Albright s dystrophy has a place among genodystrophic diseases and his name should be preserved in this connection

Idiopathic Hypoparathyroidism Presenting as Psychosis and Complicated by Chlorpromazine Jaundice is described by Bernard J B Yim and John R Jaenike[6] (Univ of Rochester)

Woman 59 was treated for increasing anxiety depression and paranoia with phenobarbital chlorpromazine and reserpine Jaun dice resulted which was considered to be due to chlorpromazine She became delirious and disoriented and showed moderate rigidity of the extremities and trunk On the ECG the Q T was prolonged Serum calcium was 4 2 mg /100 ml Phosphorus was 8 mg /100 ml The EEG showed a basic frequency of 8/second with diffuse moderate slow ac tivity of 5 6/second and paroxysmally slow activity of 4-6/second in all leads Hyperventilation had no effect The Chvostek sign was present Treatment was begun with oral calcium gluconate and dihy drotachysterol The patient had two generalized convulsions the day after therapy was started and another 3 days later Vitamin D and Amphojel[8] were added to the regimen Serum calcium subsequently rose progressively with concurrent improvement in the sensorium and regression of abnormal laboratory values No increase in phos

(6) Am J M d 5 478-493 S pt mber 1958

Serum magnesium levels were determined up to 2 months after surgery. In most experiments serum calcium, potassium and sodium values were also determined simultaneously. Serum magnesium levels were altered significantly only by adrenalectomy and thyroparathyroidectomy.

It appears that aldosterone might be a regulatory hormone for serum magnesium as it is for serum sodium and potassium. Under normal conditions at least 95% of the filtered magnesium is reabsorbed by the tubules. If aldosterone is necessary for regulation of reabsorption of magnesium, removal of the adrenal glands should result in less urinary excretion and higher blood levels of magnesium. The effect of adrenalectomy on serum magnesium appears to be identical with its effect on serum potassium. That hypophysectomy did not alter magnesium levels gives additional support to this concept. This observation agrees with the prevailing view that aldosterone secretion and activity are independent of the pituitary.

Removal of thyroids and parathyroids caused a definite alteration of serum electrolytes with low calcium and magnesium and elevated potassium levels. In no other group did magnesium reach levels so low. Tetanic convulsions began 1 week after surgery when magnesium had reached subnormal levels and ceased about 3 weeks after surgery when it had risen spontaneously to higher levels. This phenomenon could not be explained.

Serum magnesium and calcium showed identical behavior after thyroparathyroidectomy and after removal of other endocrine glands except after adrenalectomy when magnesium levels rose and calcium levels fell.

HYPERPARATHYROIDISM

Primary Hyperparathyroidism Associated with Hypomagnesemia. The importance of magnesium in human metabolism is unquestioned. It is present in amounts estimated up to 1 600 mEq. It is found in relatively large quantities in bone, functions as a coenzyme, is a major intracellular cation and is important in neuromuscular conduction for cardiac and skeletal muscle. Despite this, descriptions of definite magnesium deficiency have been limited principally to lower

reabsorption through increased urinary excretion of phosphorus. Increased urinary calcium has been assumed to be secondary to increased concentration of serum calcium. However, urinary calcium could be increased to 300 mg daily by a mere 5% reduction in tubular reabsorption. A direct effect of vitamin D and dihydrotachysterol on renal tubular reabsorption of calcium appears likely.

In the past, serum calcium levels were assumed to be satisfactory when the Sulkowitch test for urinary calcium was positive. Presence of calcium in the urine does not necessarily imply normal levels in the serum. A positive Sulkowitch test is not reliable for early detection of vitamin D or dihydrotachysterol overdosage. Absence of tetany symptoms is not a reliable indicator for absence of hypocalcemia because many patients with chronic hypoparathyroidism can tolerate low blood calcium.

Vitamin D and dihydrotachysterol apparently (1) increase absorption of calcium from the gastrointestinal tract and (2) increase bone reabsorption through increased urinary excretion of phosphorus (second action of vitamin D). A third action has been postulated: increased intestinal absorption of nitrogen, sodium, potassium and magnesium. The present data suggest a fourth action: decreased tubular reabsorption of calcium.

► [This is an important observation since many physicians have used the Sulkowitch test as an index for adjusting the dose of vitamin D or of dihydrotachysterol in the treatment of hyperparathyroidism. Our experience has been identical with that reported here, i.e., that the urine of patients taking these agents may show a strongly positive Sulkowitch reaction during hypocalcemic tetany. It should also be noted that people with hypoparathyroidism are not immune from the tetany of hyperventilation resulting from anxiety.—Ed.]

Effect of Removal of Major Endocrine Glands on Serum Level of Magnesium in Dogs was studied by Peter Weil and David State[8] (Cedars of Lebanon Hosp., Los Angeles). Knowledge of alterations of blood magnesium level in health and disease in man is still limited. Attempts have been made to correlate the serum level of magnesium with the serum levels of other electrolytes, but the findings have not been uniform.

In the authors' investigation, the adrenals, thyroids and parathyroids, gonads, pituitary and pancreas were removed

(8) Surg Gynec & Obst 10[illegible]: 483-48[illegible], Oct, 1958

seems plau ible since the effect of the low serum magnesium concentration on neuromuscular conduction may have more than counterbalanced the known depressant effect of hyper calcemia and hypokalemia

Parathyroid hormone which effects bone dissolution and a phosphate diuresi may reduce body magnesium stores Urinary data in the fir t patient (Fig 15) show that magne sium losses paralleled tho e of calcium and phosphorus In the second patient it is rea onable to assume that postoper ative accretion of bone and soft tissue minerals including magnesium may have accounted for the continuance of hy pomagnesemia for 6 weeks postoperatively

If these speculation are correct hypomagnesemia and the attendant symptoms should be observed more often in hy perparathyroidism than is indicated by previous reports The clue to the pre ence of hypomagnesemia may be occur rence of tetany after surgical correction of hyperparathy roidism that is refractory to administration of large amounts of calcium

► [In the foregoing and following stud e hypomagne emia was clearly demonstrated during the period of active hyperparathyroidism Since hypo-magne emia occurs non pecifically in many conditions in which dietary intake is increased or urinary loss is accelerated one cannot help wonder ing whether it is specifically related to the hyperparathyroidism or the result of one of its complications —Ed]

Magnesium Studies in Relation to Hyperparathyroidism were undertaken by Benjamin A Barnes Stephen M Krane and Oliver Cope[1] (Harvard Med School) in view of the chemical similarity of magne ium and calcium The technic for measuring magne ium was that of Garner which uses acid extracts of ashed pecimens and coupling of the magne sium ion with titan yellow

A man 37 underwent two operations (one exploratory and one definitive) for removal of a hyperfunctioning ade noma Before removal balances of nitrogen magnesium phosphorus and calcium were negative and loss of magne sium was excessive in relation to nitrogen The actual and hypothetical losses of phosphorus were in good agreement in the preoperative periods During the operations the ancil lary factors of anesthesia analgesia and bed rest were iden

(1) J Cl E docri 1 17 1407 14 1 Dec be 19

animals Manifestations include vasodilatation hyperirritability of the nervous system cardiac arrhythmia generalized spasticity and fatal tonic clonic convulsions

Conclusive evidence of a clinical syndrome related to deficiency of magnesium in man is lacking James W Agna and Richard E Goldsmith[9] (Univ of Cincinnati) recently observed 3 patients who in the course of adenomatous hy

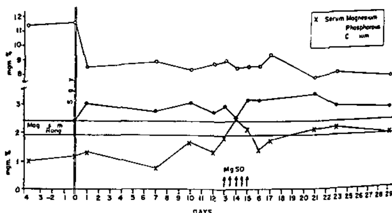


Fig 15 —Serum magn um ph phoru d l m l s bef e and after ex on f p thy d d n m l t p t t St ppl d rep e t n m l ra g r se m m gnes m v l (C t y f Agn J W and G ldsm th R E New E gl d J M d 258 2 5 J n 30 1958)

perparathyroidism proved by surgical exploration showed clinical abnormalities believed to be related to magnesium deficiency

The first 2 patients had symptoms of neuromuscular irritability and paresthesias that appeared to be associated with hypomagnesemia (Fig 15) Administration of magnesium sulfate caused reversal of symptoms and clinical improvement in each was associated with a return to normal serum magnesium concentrations In the first patient abnormalities of the ECG also became normal during magnesium therapy Although no other serum electrolyte abnormalities were present just before administration of magnesium sulfate the abnormal ECG cannot be considered specific for magnesium deficiency

Whether hypomagnesemia accounted for presence of hyperreflexia in the third patient is speculative However it

(9) N w E l d J Med 258 5 J 30 1958

for more than 10% of our cases Not only the symptoms enumerated but loss of weight, thirst dryness polyuria hyponatremia and hypokalemia are frequent. Hypercalcemia from any cause produces the same syndrome in which gastrointestinal disturbances or impaired renal function may dominate the clinical picture Besides anorexia, nausea and vomiting peptic ulcer is surprisingly common in hyperparathyroidism Brummer and Kasanen (Acta med scandinav 172 245 19 8) were unable to find chemical evidence of hyperparathyroidism in 50 patients with gastrointestinal distress and I note that Flack (Am J Surg 96 613 19 8) states that screening of patients with peptic ulcer for hyperparathyroidism so far has not proved rewarding We have however seen 2 patients in whom the only clinical symptom was refractory peptic ulcer For a careful study of the effect of hyperparathyroidism on renal function the interested reader is referred to C A Edvall (Acta chir scandinav supp 229 1958) —Ed]

Serendipity in Diagnosis of Primary Hyperparathyroidism Classically primary hyperparathyroidism is manifested by symptomatic complications involving the skeleton or urinary tract However hyperparathyroidism may cause atypical symptoms or be present without symptoms In such instances diagnosis may be made by serendipity—the fortuitous discovery of valuable things Raymond V Randall and F Raymond Keating Jr[3] (Mayo Clinic and Found) report on 20 patients in whom the diagnosis was made unexpectedly during investigation of unrelated conditions Each patient showed elevated concentration of serum calcium that reverted to normal after removal of a parathyroid tumor In 4 a parathyroid tumor was found during an unrelated operation In 9 elevated concentration of serum calcium was noted although the determination had been done to rule out presence of hypocalcemia In 7 nephrocalcinosis renal calculi or generalized demineralization of the bones was incidentally noted in x rays for unrelated conditions

CASE 1—Woman 40 at operation for a thyroid nodule showed a grade 1 papillary and follicular adenocarcinoma During operation a parathyroid adenoma consisting of chief and transitional water clear cells was noted in the usual position of the right inferior parathyroid gland Blood obtained during operation showed the following value calcium 11 4 mg and phosphorus 2 5 mg /100 ml 2 days after operation the values were calcium 8 2 mg and phosphorus 2 6 mg /100 ml Questioning after operation revealed a history of renal colic and passage of a stone about 5 years previously

CASE 5—Boy 18 with a convulsive disorder for 5 years was hospitalized Values for serum calcium determined several times varied between 13 1 and 16 1 mg and for phosphorus between 2 1 and 2 4 mg /100 ml At operation a parathyroid adenoma weighing 300 mg and consisting of chief cells was found in the usual region On the 3d

(3) Am J M S 236 5 5 589 Novembe 19 8

tical the only alteration was excision of the adenoma in the second procedure

After removal of the tumor the negative nitrogen magnesium phosphorus and calcium balances were reversed The *initial* loss of magnesium was greater than could be explained by nitrogen deficit due to catabolism of soft tissue and the relatively positive magnesium balance after tumor removal could not be explained on the basis of formation of soft tissue with a composition similar to skeletal muscle Comparison of the data for both operations showed that the pronounced renal *conservation of magnesium after tumor removal* could not be ascribed to anesthesia or other features of the surgical procedure The changes noted were presumably associated with decreased amounts of circulating parathyroid hormone

Hypercalcemic Crisis Due to Hyperparathyroidism A potentially fatal course characterized by rapidly progressive *nausea vomiting lethargy* and azotemia is *occasionally* seen in patients with hyperparathyroidism Three patients with these manifestations are described by William C Thomas Jr John G Wiswell Thomas B Connor and John E Howard (Johns Hopkins Univ) In 2 recognition was sufficiently prompt and emergency removal of a parathyroid adenoma resulted in a successful outcome in each In the third patient the correct diagnosis was suspected only 2 hours before death At autopsy a large parathyroid adenoma was found

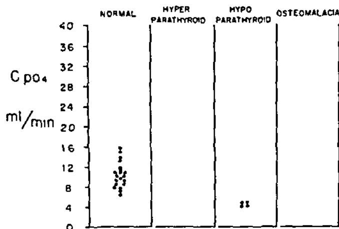
The clinical manifestations enumerated occur with marked hypercalcemia of any etiology Although the pathogenesis of this syndrome is not clearly understood successful treatment seems dependent on prompt reduction of the high serum calcium concentrations Correction of dehydration with parenteral fluids may improve the clinical status of some patients with hyperparathyroidism exhibiting these features but it may be insufficient to alter the progressive course as was demonstrated in the 2 patients undergoing operation *Although cortisone and corticotrophin lower the serum calcium concentration* in most hypercalcemic states the hypercalcemia due to hyperparathyroidism has not been corrected by treatment with these hormone

► [This increasingly frequent syndrome of hyperparathyroidism accounts

(2) A J Med 24 229 35 February 1958

patients with hypoparathyroidism the phosphate clearance was diminished ranging from 1 7 to 7 3 ml/minute In 5 patients with osteomalacia it was significantly elevated

Intravenous administration of 200-400 units of parathyroid extract caused significant increase in phosphate clearance in normal subjects and in patients with hypoparathyroidism but no appreciable elevation in patients with uremia Therapy with vitamin D_2 caused no apparent change



F g 16 —Comp ison f ph ph t l n n hype p athy o d m hypoparathy d m d t om l w th th t f n rmal bjects (Courte y of Kyl L H *et al* Am J Med 24 40 48 F bru y 1958)

in pho phate clearance despite normalization or near normalization of blood calcium and phosphorus levels in these patients

The finding of low phosphate clearance in the presence of a lowered ratio of filtered to reabsorbed phosphorus would point to renal di ease rather than hyperparathyroidism The presence of a normal or only slightly depressed phosphate clearance in conjunction with azotemia and a low TRP should heighten suspicion of parathyroid hyperfunction

Changes in phosphorus intake materially influence tests of parathyroid function including the phosphate clearance This is of particular importance in patients who may be taking aluminum hydroxide (which suppresses phosphate reabsorption in the intestine) or are on a low calcium diet

postoperative day values were serum calcium 10 mg and phosphorus 3 4 mg /100 ml Questioning revealed that the patient had had some weakness fatigue polyuria and polydipsia

CASE 6—Woman 34 showed episodes manifested by *blurring of* vision and on several occasions had lost consciousness Serum calcium value varied between 12 1 and 13 6 mg /100 ml After fasting for 26 hours she showed unusual behavior and slightly slurred speech Blood *sugar value was then 29 mg /100 ml She had 2 operations for* islet cell adenoma s About 10 months later a parathyroid adenoma 1 cm in diameter was found in the usual region of the right inferior para thyroid The other parathyroids were not identified during operation After operation the serum calcium level was 10 1 mg /100 ml but in a few days it started to rise again and 11 years later was as high as before parathyroidectomy At a second exploration of the parathy roids a parathyroid adenoma was found on the right The left supe rior parathyroid was enlarged three or four times its normal size and it too was removed When the patient was first seen she howed no skeletal or renal disease but 13 years later stones had developed in the urinary tract and she showed a duodenal ulcer

CASE 9—Woman 46 had back pain X rays of the lumbar spine *revealed hypertrophic changes whereas the skull and right hand* showed demineralization suggesting hyperparathyroidism Serum values were calcium 14 8 16 3 mg and urea 92 mg /100 ml Explo ration disclosed a parathyroid adenoma Six months after operation serum values were calcium 10 1 phosphorus 3 6 mg and urea 48 mg /100 ml Blood pressure was 210/130 mm Hg

CASE 18—Woman 55 had tinnitus for 6 months and also pare the sias Serum calcium values were 10 8 11 3 mg /100 ml At operation a parathyroid adenoma was found 2 days later the serum calcium had dropped to 9 6 mg /100 ml

Phosphate Clearance in Diagnosis of Parathyroid Dys function Laurence H Kyle Marcus Schaaf and John J Canary[4] (Georgetown Univ) evaluated phosphate clearance as a possibly more practicable test than per cent tubular re absorption of phosphate (TRP) which requires accurate creatinine determinations and is not applicable for use in hypoparathyroidism where *TRP* is usually maximally elevated

Phosphate clearance in normal subjects was compared with that noted in patients with various types of parathy roid dysfunction (Fig 16) In 25 normal subjects the mean phosphate clearance was 10 8 ± 2 7 ml /minute In hyper parathyroidism the phosphate clearance was elevated in all but 1 *patient* who had renal failure with uremia and an en dogenous creatinine clearance of only 30 ml /minute In 10

(4) Am J Med 4 40 48 Feb y 19 8

► [The diagnosis of concurrent hyperparathyroidism and sarcoidosis is a brilliant clinical coup I note that an important clue was provided by the Thomas test namely the failure of cortisone to reduce the hypercalcemia to normal (J Lab & Clin Med 52 11 1958) We too have found this a valuable adjunct in 8 cases of hyperparathyroidism though in 1 of our patients with a surgically proved parathyroid adenoma the serum calcium level fell from 12 2 mg /100 ml to normal after administration of 180 mg hydrocortisone daily for 7 days In still another patient with all the chemical abnormalities typical of hyperparathyroidism administration of prednisone 60 mg /day caused all the abnormalities to disappear entirely and they have remained absent for 5 months Despite these rare exception the test is an extremely important and useful aid —Ed.]

Hereditary Hyperparathyroidism Associated with Recurrent Pancreatitis is reported by Charles L Jackson[6] (Bluffton Ind) In a study of 4 generations of one family there were 7 cases of hyperparathyroidism spanning 2 generations and associated with recurrent pancreatitis in at least 2 instance (Fig 17) Hyperparathyroidism in this family followed an autosomal dominant pattern

Man 29 (Fig 17 *III 2*) was originally seen with abdominal pain nausea and vomiting at which time the serum amylase was 250 units Edema of the pancreas and omentum was found at laparotomy without evidence of hemorrhagic necrosis Serum calcium at this time was 13 14 mg /100 ml The pancreatitis was recurrent and the glucose tolerance curve changed from normal to mildly diabetic Diffuse calcification of the pancreas but not of the kidneys was found at x ray Skull x rays showed diffuse rarefaction of the calvarium Dental x rays were normal A solitary 5 Gm adenoma of the right lower parathyroid was removed followed in time by cessation of the abdominal pain and nausea

Man 27 (Fig 17 *III 5*) had recurring abdominal pain nausea and vomiting and a high serum amylase content (830 units) Hypercalcemia (13 mg / 100 ml) was found but no calcification in pancreas or kidneys The lamina dura was absent A 5 Gm solitary adenoma of the right lower parathyroid was excised In the 11 months following operation he had no further episodes of abdominal pain nausea disappeared and a marked decrease in nervous irritability was noted

The relief of symptoms of recurrent pancreatitis by parathyroidectomy in this study and elsewhere suggests that the pancreatitis was in some way sequentially related to the hyperparathyroidism The most attractive theory would seem to be that pancreatitis is secondary to stone formation in the pancreatic duct system as a result of hypercalcemia and alkaline pancreatic secretion The possibility cannot be excluded that hereditary pancreatitis coexist with hyper

(6) A I t M d 49 8 9 36 O b 19 8

Measurement of the phosphate clearance i a valuable screening test for hyperparathyroidism and of diagnostic aid in parathyroid deficiency

Hyperparathyroidism in Identical Twins One of Whom Suffered Concomitantly of Boeck s Sarcoidosis I Snapper J J Yarvis H Robert Freund and Arthur I Goldberg[5] (Beth El Hosp Brooklyn) discuss the problems of differential diagnosis

Man at age 29 had onset of fever, arthralgia (without swelling or redness) in both large and small joints generalized tender lymphadenopathy and splenomegaly Lymph node biopsy later confirmed by skin biopsy showed reticuloendotheliosis and a sarcoid like reaction Subsequently the symptoms progressed and the findings included polyuria liver enlargement nodular densities throughout both lung fields mild generalized bone resorption and nephrolithiasis (calcium phosphate) The lamina dura was intact About this time the patient s twin was operated on for hyperparathyroidism Reconsideration of the symptoms in the present patient suggested that the hypercalciuria hypercalcemia (15 15 5 mg /100 ml) nephrocalcinosis nephrolithiasis and pseudo diabetes insipidus might be due to hyperparathyroidism rather than to sarcoidosis

For differentiation the effect of cortisone on calcium metabolism was investigated The hypercalcemia and hypercalciuria did not revert to normal values after steroid therapy suggesting they were due to hyperparathyroidism rather than sarcoidosis In sarcoidosis the hypercalcemia and hypercalciuria are possibly due to increased absorption from the intestines (as in hypervitaminosis D) and this effect may be blocked by steroid administration The diagnosis of hyperparathyroidism was abetted by the demonstration of a remarkably low serum phosphorus (1 7 1 8 mg /100 ml) level in the patient

A parathyroid adenoma was excised after which the joint pain polyuria polydipsia postprandial distress and heartburn disappeared The hepatosplenomegaly remained however Subsequently the sarcoidosis was reactivated and steroid therapy was resumed

The twin had had a parathyroid adenoma removed at age 33 (2 years before the present patient s operation) He died of bleeding esophageal varices secondary to hemangioma of the liver and it was not known whether he had had sarcoidosis

The few previously reported cases of familial hyperparathyroidism were reviewed by the authors In these the adenomas were often found to be multiple with an earlier onset of symptoms than commonly seen Hypercalcemia was usually marked and many cases presented the classic symptoms of osteitis fibrosa cystica generalisata (Recklinghausen disease)

(5) M t J J m 7 671 680 N mbe 1958

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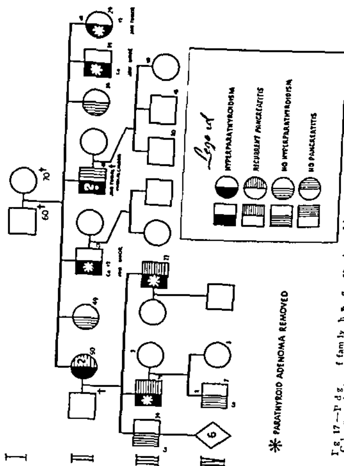
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(6) A Int Med 49 829-836 Oct 1958



parathyroidism in this family with the latter causing the underlying pancreatitis to be more completely manifest

Primary Hyperparathyroidism and Metastatic Breast Carcinoma Case in Which Breast Carcinoma Metastasized to Parathyroid Adenoma is reported by Lewis B Woolner F Raymond Keating Jr and B Marden Black[7] (Mayo Clinic and Found)

Woman 54 who 10 years previously had had nephrocalcinosis was hospitalized for severe chest pain One year previously cholecystec

(7) Cancer 11 975 979 Sept Oct 1958

tomy was done for cholelithiasis uremia was present at that time and nephrocalcinosis was again noted A month later radical mastectomy was done for carcinoma of the breast and 2 months after this operation bony lesions that were assumed to be metastatic were demonstrated A series of x ray treatments for the bony lesions followed and a few months later testosterone propionate injections were given for about 5 months

Blood pressure was 130/86 Hirsutism acne and moderate clitoridal enlargement were noted Proteinuria hematuria and pyuria were present The hemoglobin value was 10 6 Gm /100 ml Other blood values were CO_2 combining power 16 mEq /l urea 86 mg calcium 13 2 mg inorganic phosphorus 3 2 mg alkaline phosphatase 13 1



Fig 18 —Metastat ... with ... H ... Su ... m ×110 (C ... y of Wool ... L B ... Can ... 11 974 977 S ... Oct 1958)

Bodansky units and creatinine 2 2 mg /ml X rays showed extensive osseous changes many cystic areas fibrous degeneration and subperiosteal resorption particularly in the fingers Many of the ribs were distorted by expanding and osteolytic lesions The skeletal disease was interpreted as metastatic carcinoma superimposed on osteitis fibrosa cystica resulting from hyperparathyroidism

A parathyroid tumor was excised from the superior strait of the thorax Part of the mass was a parathyroid adenoma surrounded by a rim of normal parathyroid tissue Mitotic figures were not seen in the adenoma In sharp contrast to the background of small regular parathyroid chief cells extensive deposits of metastatic carcinoma were noted within the adenoma (Fig 19) making up about a third of its bulk The carcinoma cells were large and hyperchromatic and showed variations in size and shape with areas of necrosis and numerous mitoses Histologically the metastatic tissue was identical with that of the carcinoma of the left breast and left axillary lymph node previously removed

Differential diagnosis between these two disorders of

bone and calcium metabolism may be difficult The pathognomonic x ray features of primary hyperparathyroidism with osteitis fibrosa cystica include characteristic subcortical cysts and subcortical bone resorption These features are never seen in typical carcinomatosis ossei The ground glass appearance of the skull and mandible are unlikely to occur in simple carcinomatosis ossei In many other facets the bone changes and laboratory findings are remarkably similar in the two disorders

► [This is a unique site of metastasis The diagnosis of hyperparathyroidism is particularly difficult in the presence of breast cancer since hypercalcemia is so common in advanced cases (25.5% of our series) In contrast to hyperparathyroidism the hypercalcemia of breast cancer is not accompanied by a low rate of tubular reabsorption of phosphate though the serum phosphate level may be low normal or high The question arises of the propriety of subjecting a patient with advanced breast cancer to operation for a possibly harmless parathyroid adenoma We have not hesitated to do so in 2 cases and in both invalidism was greatly reduced after adenomectomy Since breast cancer can be extremely indolent coincident symptomatic diseases probably should be treated as if the patient had no malignancy The hypercalcemia of breast cancer frequently responds to administration of fluids or of cortisone unlike that of hyperparathyroidism in which the serum calcium level rarely fluctuates except in instances of acute hypercalcemia when hydration and mobilization effect a decrease Howard has also reported a case of hyperparathyroidism in which the serum calcium level dropped to normal following infarction of the adenoma (J Clin Endocrinol 13 997 1953) Our experience has not been in accord with that of Whitby who described intermittent overactivity of a parathyroid adenoma (Lancet 1 883 Apr 26 1958) —Ed.]

Primary Chief Cell Hyperplasia of Parathyroid Glands New Entity in Surgery of Hyperparathyroidism Oliver Cope W Milo Keynes Sanford I Roth and Benjamin Castleman[8] (Boston) report that since 1952 10 patients with primary hyperparathyroidism have been noted with a type of parathyroid hyperplasia distinct from adenoma carcinoma and the previously described water clear cell hyperplasia All parathyroid glands were enlarged by the disease process and the cells were predominantly of the nonvacuolated chief cell type The entity is called primary chief cell hyperplasia

It is essential that the entity be recognized at operation if secondary operations are to be avoided The enlargements are most readily confused with adenoma especially if only 1 gland is exposed Of the first 200 patients with primary hyperparathyroidism cared for at the Massachusetts General

(8) Ann Surg 148 375 388 September 1958

Ho pital 5% showed this primary chief cell hyperpla ia

Of the 10 patients with primary chief cell hyperpla ia 4 also had tumors of the pancreas and pituitary gland and it is pos ible that this condition previously described as ade nomatous hyperplasia and multiple adenomas will prove to be the common type of parathyroid disease in patients with multiple endocrine abnormalities

Gro sly the cut surface of the individual glands present ill defined nodularity that is more evident microscopically



Fig 19—P m y h f ll hype pl N t t f ll l p tt (C u t f C p O r l A S g 148 375 388 S pt mb 1958)

(Fig 19) The gross and microscopic appearance of a single gland may be insufficient to distinguish chief cell hyper plasia from an adenoma and examination of all 4 glands may be necessary to establish definite diagnosis Surgical treatment consists of total resection of 3 glands and subtotal resection of the other

[The fact that 8 of the e 10 patients did not have uremia suggests that the hyperplasia was indeed primary In ad lition it is difficult to under stand why secondary hyperplasia such as that of uremia should cause hypercalcemia During the meeting at which this paper was discussed Goldman described 4 of our ca e in which the diagnosis of primary hyper

plasia was less certain since 3 of the patients were uremic. Whether this entity is part of the syndrome of multiple endocrine adenomatosis can also be asked.—Ed.]

THE HYPERCALCEMIAS

Milk Alkali Syndrome: Hypercalcemia, Alkalosis and Azotemia Following Calcium Carbonate and Milk Therapy of Peptic Ulcer. Symptoms usually begin 3-8 days after therapy is begun, with distaste for milk, excessive dryness of the mouth and pharynx, anorexia, dizziness, headache, weakness or lethargy, nausea and occasionally vomiting. Conjunctivitis, disorientation, mental confusion, psychotic reactions and stupor have been noted. Julius Wenger, Joseph B. Kirsner and Walter L. Palmer[9] (Univ. of Chicago), reviewing the records of about 3,500 patients hospitalized with peptic ulcer during 1947-56, found 35 in whom the syndrome developed. Daily intake of calcium carbonate had not been precisely measured; 2-4 Gm. 10-15 times daily was prescribed and the daily intake was estimated as 20-50 Gm.

In 18 patients the first indication was nausea. The mean serum calcium level when first determined on the 4th-6th day of symptoms was 14.7 mg./100 ml. When calcium carbonate therapy was stopped, the serum calcium level fell to an average of 12.3 mg./100 ml. on the 12th day. Four days after therapy was stopped, the phosphorus level had decreased slightly to a mean of 3.2 mg./100 ml., and it continued to decrease to a mean of 2.8 mg./100 ml. by the 16th day of symptoms. Serum bicarbonate content averaged 38.2 mM./L.

Azotemia ranged from mild in 1 or 2 patients to levels of 129 and 138 mg./100 ml. in 2 others. The mean value of blood urea nitrogen, 57.9 mg./100 ml., decreased by the 10th day of symptoms to 46.1 mg./100 ml. and reached normal values by the 23d day. Urinary pH rarely was dependable as an index of alkalosis, though the urine tended to be alkaline.

Moderate hypertension was noted in 14 patients before development of the syndrome. In 23 patients, diastolic pressures exceeded 90 mm. during the episode and the trend was toward moderate elevation of blood pressure during the height of azotemia. In only a few patients did hypertension

(9) G t nt ol gy 33 45 769 N mb 1957

persist after hypercalcemia subsided Specific ophthalmologic examinations for calcium deposits in 15 patients revealed abnormalities in 6

Usually calcium carbonate was discontinued when diagnosis of hypercalcemia was established Additional therapy generally included intravenous fluids isotonic salt solution ammonium chloride and 5% dextrose in distilled water Seven patients received calcium carbonate for varying periods after recovery from the acute episode without recurrence of the syndrome and 4 continued the antacid during the episode without untoward effects recovering as rapidly as those in whom the antacid was discontinued

Of the 35 patients 16 had definite histories of pre existing hypertension and some of these had depressed renal function Chronic renal disease was present in 4 nephrolithiasis in 2 and benign prostatic hypertrophy in 2 Gastrointestinal hemorrhage also seemed to be an important contributory factor presumably because of decreased blood flow to the kidneys Eight patients had moderate gastrointestinal hemorrhage immediately preceding hypercalcemia Of the 35 patients only 1 showed the syndrome without obvious predisposing cause and she had a past history of scarlet fever

Impaired renal function appears to be important in development of the milk alkali syndrome whether the impairment is due to pre existing hypertensive or renal disease dehydration alkalosis or gastrointestinal hemorrhage None of the patients showed evidence of hyperparathyroidism but this possibility has not been entirely excluded The ultimate prognosis of the acute syndrome is favorable

Thyrotoxicosis Simulating Hyperparathyroidism is reported by R A Pribek and R C Meade[1] (Marquette Univ)

In man 30 the prominent symptomatology consisted of anorexia nausea vomiting abdominal pain severe myasthenia prostration and mental changes Greatly elevated serum calcium suggested that these symptoms were attributable to hypercalcemia Primary hyperparathyroidism was suspected but the diagnosis seemed unlikely in the presence of normal serum inorganic phosphorus Diagnosis of thyrotoxicosis with hypercalcemia was made The patient was given a therapeutic trial of 400 mg propylthiouracil daily for 6 weeks and the symptoms disappeared Serum calcium returned to normal and remained normal despite persistent thyrotoxicosis Subsequently I^{131}

(1) A M A A h I t Med 100 994 997 Dec mt 1957

than was less certain since 3 of the patients were uremic Whether this entity is part of the syndrome of multiple endocrine adenomatosis can also be asked —Ed]

III HYPERCALCEMIAS

Milk Alkali Syndrome Hypercalcemia Alkalosis and Azotemia Following Calcium Carbonate and Milk Therapy of Peptic Ulcer Symptoms usually begin 3 8 days after therapy is begun with distaste for milk excessive dryness of the mouth and pharynx anorexia dizziness headache weakness or lethargy nausea and occasionally vomiting Conjunctivitis disorientation mental confusion psychotic reactions and stupor have been noted Julius Wenger Joseph B Kirsner and Walter L Palmer[9] (Univ of Chicago) reviewing the records of about 3 300 patients hospitalized with peptic ulcer during 1947 56 found 35 in whom the syndrome developed Daily intake of calcium carbonate had not been precisely measured 2-4 Gm 10 15 times daily was prescribed and the daily intake was estimated as 20 50 Gm

In 18 patients the first indication was nausea The mean serum calcium level when first determined on the 4th-6th day of symptoms was 14 7 mg /100 ml When calcium carbonate therapy was stopped the serum calcium level fell to an average of 12 3 mg /100 ml on the 12th day Four days after therapy was stopped the phosphorus level had decreased slightly to a mean of 3 2 mg /100 ml and it continued to decrease to a mean of 2 8 mg /100 ml by the 16th day of symptoms Serum bicarbonate content averaged 38 2 mM /L

Azotemia ranged from mild in 1 or 2 patients to levels of 129 and 138 mg /100 ml in 2 others The mean value of blood urea nitrogen 57 9 mg /100 ml decreased by the 10th day of symptoms to 46 1 mg /100 ml and reached normal values by the 23d day Urinary pH rarely was dependable as an index of alkalosis though the urine tended to be alkaline

Moderate hypertension was noted in 14 patients *before development of the syndrome In 23 patients* diastolic pressures exceeded 90 mm during the episode and the trend was toward moderate elevation of blood pressure during the height of azotemia In only a few patients did hypertension

(9) Gastroenterology 33 745 769 November 195

During the period under study the patient lost at least 3% of his skeletal calcium without apparent x-ray change. It is concluded that thyrotoxic bone disease is not seen more frequently because the underlying disorder is corrected before demineralization proceeds to a clinically demonstrable level.

The authors consider the possible causes of hypercalcemia and excessive excretion of calcium with thyrotoxicosis. The return to normal during euthyroidism and the amelioration after phosphorus administration suggest a direct effect of excessive thyroid hormone on skeletal metabolism with reversal or counteraction of the effect by phosphorus. The presence of hypercalcemia in this patient and in the few others described in the literature suggests a defective control on renal clearance of calcium by parathyroid secretion.

Hypercalcemic Nephropathy in Thyrotoxicosis was observed by Olle Sallin[3] (Central Hosp., Örnsköldsvik, Sweden). In a man aged 48 onset of thyrotoxicosis was soon followed by subfebrility, rapid loss in body weight, muscle weakness, vomiting and serious deterioration in health. He showed a BMR of +100%, hypercalcemia (13.5-14.1 mg./100 ml.) and anemia with hemoglobin value 64 Gm./100 ml. The nonprotein nitrogen value was 50.63 mg./100 ml. Thyrotoxicosis and hypercalcemia responded promptly to iodine and propylthiouracil. The renal functional disturbance was more persistent and anemia did not disappear until after about 4 months.

The author suggests that nausea, vomiting, renal impairment and muscle weakness are directly or indirectly due to hypercalcemia. This represents a stage of incompensation of disturbed calcium metabolism, probably of an osteoporotic nature. During this stage large amounts of calcium are shed from the skeleton into the bloodstream. Intense thyrotoxicosis of short duration and a previously fully mineralized skeleton are presumed to be necessary for development of hypercalcemia. Dehydrating factors are probably of essential significance.

Once hypercalcemia has commenced with decreased muscle tone, fatigue and increased immobilization, it decreases

(3) Acta ... 1 ... 9 4 5-434 ... 9

tudie confirmed the clinical impression of hyperthyroidism and the patient was treated with I^{131}

At present there is no satisfactory explanation for the occasional finding of hypercalcemia in thyrotoxicosis Observations by several investigators would indicate that the thyroid hormone alone can elevate the serum calcium and that coexisting hyperparathyroidism is not necessary to explain the hypercalcemia sometimes associated with thyrotoxicosis Others have suggested that the increased calcium turnover in thyrotoxicosis may be related to increased bone blood flow The presence of azotemia in this patient and in 3 of 4 previous patients suggests that renal function may be impaired in this condition This finding however may be the result of dehydration from protracted nausea and vomiting

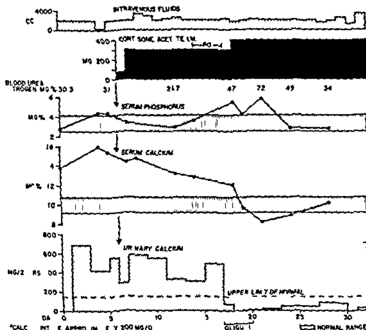
Metabolic Observations in Case of Thyrotoxicosis with Hypercalcemia are reported by Charles R Kleeman Stewart Tuttle and Samuel H Bassett (Univ of California Los Angeles)

Man 56 had had progressive anorexia abdominal complaints pruritus heat intolerance progressive weakness increasing pigmentation polyuria and polydipsia for period up to about a year The thyroid was about twice normal size firm and smooth Serum level of calcium were 11 3 13 6 and of phosphorus 3 9 4 3 mg/100 ml Alkaline phosphatase was 5 2 and 4 7 Bodansky units on two occasion Serum PBI was 17 4 µg thyroid uptake of I^{131} was 63% in 6 hours and 66% in 24 hours The BMR was +23 and +28% There was no x ray evidence of demineralization osteitis fibrosa cystica subperiosteal bone resorption or soft tissue calcification There were no renal calcification

A 125 day balance study done as the patient became euthyroid showed that the excessive urinary and fecal loss of calcium bore little relation to the diet or the level of nitrogen balance A high phosphate diet ameliorated the metabolic abnormality and corrected the hypercalcemia Successful treatment of the thyrotoxicosis produced similar changes in calcium metabolism Throughout the study the renal excretion of calcium reflected primarily alteration of the underlying osseous metabolism rather than variation in dietary calcium whereas the fecal excretion of calcium consistently exceeded dietary intake and was relatively constant regardless of the level of thyroid activity In a second portion of the study a 50 day balance study during recurrence of thyrotoxicosis the metabolic defect in the osseous metabolism was less marked Hypercalcemia was not then present Urinary calcium excretion increased only slightly over that during a euthyroid period and fecal losses were unchanged

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calcium was 15 4 mg /100 ml urinary calcium was 556 mg /24 hours (Fig 20) After use of the steroid there was gradual lowering of serum and urinary calcium over 2 weeks to levels of 9 7 mg /100 ml serum calcium and 7 mg /24 hours urinary calcium Although the hypercalcemia was successfully treated no substantial alteration oc



F g 0 —Urin y l um data d blood l vel f l m ph phorn d t og n f m n 38 with m t ta d oc rc n m pr m y u known Cal um b- rm l t es e rt i t rmal d t ime t w yr t wm (Court y of My W P L Ca e 11 83 S Ja F b 1958)

curred in the course of the illness and the patient died shortly afterward of progressive disease

The mode of action of cortisone in reducing hypercalcemia is conjectural Myers refers to pertinent literature relating to this In some of the patients relative inhibition of tumor growth rate may have been responsible although the patients died of extensive cancer Despite the absence of a clear mode of action cortisone has a useful role in management of hypercalcemia of neoplastic origin

Effect of Cortisone in Experimental Hypervitaminosis D was studied by William C Thomas Jr and H Connell

the stresses and strains on the skeleton i e the normal osteoblastic activator with subsequent inactivity osteoporosis Anemia probably reflects the markedly negative nitrogen balance

Vitamin D Intoxication Report of Two Cases Treated with Cortisone is presented by John V Verner Jr Frank L Engel and Harry T McPherson[4] (Duke Univ) Both patients were elderly adults presenting clinical syndromes of mental confusion dehydration polyuria and hypokalemic alkalosis Each had received intoxicating doses of vitamin D from druggists without a physician s prescription Neither could give a history of vitamin D ingestion Hematologic examination revealed hypercalcemia normophosphatemia hypokalemia and azotemia Because of the suspicion of hyperparathyroidism in 1 patient surgical exploration of the neck was performed but no parathyroid adenoma was found Diagnosis in both cases became obvious when it was subsequently learned from a local pharmacist that 1 patient had been taking 200 000 units of vitamin D daily for 1 month before admission and the other up to 300 000 units daily intermittently for 3 years Cortisone therapy 200 mg/day resulted in improved mental status in 48 hours Serum calcium returned to normal in 8 and 13 days respectively In each patient the response to cortisone was prompt lasting and free from serious complications Large fluid intakes and potassium supplements were necessary throughout therapy in these patients

Cortisone in Treatment of Hypercalcemia in Neoplastic Disease has been evaluated by W P Laird Myers (Sloan Kettering Inst) who found it useful in 5 of 11 patients The patients had various types of neoplasms all but 1 had demonstrable bone metastases Treatment was with hydrocortisone cortisone or prednisone The response in all who responded appeared within 2 weeks in general longer periods of treatment did not increase the chances for obtaining a positive effect The route of administration had no consistent effect

Man 38 had metastatic adenocarcinoma involving the spine and pelvis with pulmonary infiltrations Before use of cortisone serum

(4) Ann Int Med 48 65 773 Apr 1958
(5) Ca 11 81 88 J Feb 1958

rocalcinosis spasmophilia and cataracts Decalcification of bone the most common (6 cases) is of renal origin second ary to urinary loss of calcium and appears late Urinary lithia is was noted in 4 patient but none showed nephro calcinosis

Nervous signs have not received much study In most cases asthenia is marked and often is the presenting com plaint Anxiety nervousness and some instability are always present Sometimes lo s of calcium is accompanied by changes in neuromuscular excitability of a type observed in chronic tetany or spasmophilia In 14 patients hyperexcit ability was manifested by a positive Chvostek sign In 4 of 6 electromyograms doublets or triplets were noted Two patients showed transient hypocalcemia

Cataract was noted in 7 patients In 3 these lenticular opacities (zonal subcortical posterior) were accompanied by chronic spasmophilia Nervous excitability of spasmophil ic type and cataracts may develop early and probably should be considered associated signs rather than complications They probably are related to the same disturbance of cal cium balance as hypercalciuria and represent a generaliza tion of the process Neverthele s hypercalciuria itself can aggravate the disequilibrium and consequently intensify re tention of calcium in nerves or lens

It seems probable that idiopathic hypercalciuria is due to a functional anomaly of the renal tubule which renders it hypersensitive to agents which physiologically increase cal cium and hyposensitive to those which inhibit it There are apparent rhythmic fluctuations due to intercurrent epi odes such as pregnancy menopause hyperthyroidi m and treat ment with vitamin D all of which exaggerate the loss of calcium

Treatment is on the whole di appointing but an attempt should be made to counteract the condition in order to avoid serious complications Mea ures to prevent lithiasis include dietary restriction of calcium and intestinal precipitation of calcium by aluminum gels and sodium phytate and preven tion of calcium precipitation by diuretics magnesium and acidifying agents Some authors believe that it is impossible to prevent lithiasis and direct treatment toward prevention of o teomalacia by administration of calcium and vitamin D

Morgan[6] (Johns Hopkins Univ.) Hypercalcemia is the recognized complication of overdosage with vitamin D and cortisone is sometimes effective in reducing the concentration of serum calcium in this as well as in other hypercalcemic states.

Rats given 50 000 units/kg. vitamin D daily for 7-14 days showed hypercalcemia and metaphysial sclerosis. Larger doses (100 000-400 000 units) promoted formation of excess osteoid tissue and there was an accompanying increase in histologic evidence of active bone resorption. In bones of rats given cortisone (50 mg./kg.) the metaphyses were dense and cartilage cell proliferation was reduced. However concomitant administration of cortisone with vitamin D did not lessen the vitamin D induced hypercalcemia and bones from rats so treated showed the combined effects of both compounds. The results suggest that cortisone and vitamin D act independently rather than competitively on bone in rats.

The Hypercalciurias

Idiopathic Hypercalciuria With Special Reference to 28 Personal Cases. H. P. Klotz, M. Tutin and P. Kobel[7] (Paris) report a study. Average level of calcium in the urine was about 330 mg./24 hour on a normal diet. Blood calcium levels were normal in all but 1 patient who showed transitory hypocalcemia. Average blood phosphorus level in 16 determinations was 3.2 mg./100 ml. but the level was increased in a few patients and definitely decreased below 3.0 mg. in 8. Nine patients in whom detailed study of renal function was made showed no evidence of tubular nephritis. In 2 an anomaly was associated with tubular disturbance: 1 showed a lowered renal threshold for glucose, thus presenting renal and calcium diabetes, and 1 showed markedly abnormal ammonia excretion. In idiopathic hypercalciuria all renal function tests are normal; the picture changes when renal insufficiency supervenes with secondary lithiases.

Four types of syndromes may accompany idiopathic hypercalciuria: osseous decalcification, urinary lithiasis and neph

(6) E loc n I gy 63 57-64 J l 19 8
( ) S h p P 34 53 60 O t 28 1958

24 who were not operated on but in whom serum calcium levels were usually normal (8 5 10 5 mg /100 ml) Although the authors have observed at least 3 women with renal stones due to unexplained hypercalciuria they are not in cluded because the syndrome primarily involves males and because the women presented somewhat different minor findings Among 150 proved cases of mild hyperparathyroid ism the 14 patients having the lowest serum calcium levels were chosen 13 of these were females Comparison of serum calcium serum phosphorus and 24 hour urinary calcium ex cretion in these patients with those who had idiopathic hy percalciuria elicits the point that despite lower average serum calcium levels the average urinary calcium excretion was actually higher in patients with idiopathic hypercalciuria (283 mg as compared with 269 mg /24 hours) The aver age serum phosphorus in the patients with idiopathic hyper calciuria was very nearly the same low value as that found in the 14 cases of hyperparathyroidism (2 8 vs 2 6 mg /100 ml) The prevalence of urinary tract infection was high al though no characteristic organism was found Stone analysis showing a high incidence of calcium oxalate and calcium phosphate without magnesium and ammonium phosphate strengthens the thesis that the stones were from the same cause as those in hyperparathyroidism i e hypercalciuria rather than an alkaline urine and that most were formed while urinary infection was not present

Balance studies in 4 patients demonstrated increased cal cium absorption Sodium phytate given orally reduced cal cium absorption and urinary calcium to normal levels This preparation will thus prevent stone growth and recurrence in the syndrome of idiopathic hypercalciuria

There are various possible mechanisms responsible for the development of idiopathic hypercalciuria This syndrome must be listed with hyperparathyroidism osteoporosis Cushing's syndrome steroid therapy hypervitaminosis D sarcoidosis beryllium poisoning renal osteomalacic states hyperthyroidism metastatic cancer multiple myeloma and others as being associated with increased calcium in the urine

Endocrine therapy aimed at restoration of tubular absorption of calcium has been tried with Lugol s solution and testosterone Among 9 patients treated with 40 drops of 5% Lugol s solution for 1 2 months results were unsatisfactory in 6 in 1 calcium excretion fell from 360 mg to 180 mg/24 hours and 1 showed relative improvement that could not be evaluated Among 8 treated with testosterone there were 5 failures and 3 successes In 1 decrease in calciuria coincided with improvement in renal functional tests (para aminohippurate clearance increased from 270 to 627)

In idiopathic calciuria search should be made not only for lithiasis and osteomalacia but also for cataract and tetany In all cases of spasmophilia idiopathic hypercalciuria should be suspected and this should be considered in treatment with vitamin D which often increases calciuria

► [In the previous and following papers attention is called to a laboratory finding which I believe is extremely common namely hypercalciuria in the presence of nephrolithiasis Flocks has pointed out the frequency of this finding as early as 1940 and in our laboratory it is so usual that we no longer consider it of diagnostic value in trying to decide whether the patient ha hyperparathyroidism Of greater complexity is the fact that ome of these patients have a low serum phosphate level and a low rate of tubular reabsorption of phosphate One wonders whether this might be a form of hyperparathyroidism in which the parathyroid elaborates a phosphaturic hormone without a hypercalcemic component We believe not since thorough chemical studies in 13 such cases showed no other stigmas of hyperparathyroidism by any criteria we could devi e such as skeletal dynamics measured by strontium response to phosphate restriction and exploratory operation in 1 —Ed]

Idiopathic Hypercalciuria was accompanied by a normal serum calcium level low serum phosphorus concentration and kidney stones in 35 male patients reported on by Philip H Henneman Patricia H Benedict Anne P Forbes and H Robert Dudley[8] (Harvard Med School) The syndrome shares many features with hyperparathyroidism and the only distinguishing chemical feature is the normal serum calcium as opposed to the hypercalcemia in hyperparathyroidi m Because of occasional variations in serum calcium levels idiopathic hypercalciuria cannot be definitively diagnosed unless all 4 parathyroid glands are found normal on exploration of the neck

The cases described were selected to include 11 patients in whom no parathyroid adenomas were found at operation and

(8) N w E gl nd J M d 259 80 807 O t 3 1958

whom treatment had been discontinued for 3-12 weeks received a second course. The urinary calcium excretion again fell significantly, averaging 47.9% less than in the second pretreatment control period. There was also a mean reduction in urinary phosphorus excretion of 26.2% during treatment.

Fecal calcium and phosphorus excretion (measured in 3 patients) and urinary creatinine and 17-hydroxycorticosteroid excretion showed no sustained significant change. In 2 patients mild jaundice developed but cleared promptly when Nilevar® was withdrawn. Other side effects of the drug were minimal.

CARBOHYDRATE METABOLISM

► The use of oral hypoglycemic agents as a substitute for insulin injection has now become an established part of the treatment of diabetes mellitus. The first clinically effective agent, carbutamide (BZ 55), has now been joined by tolbutamide (Orinase®), chlorpropamide (Diabinese) and metahexamide (Euglycin or Melanex). These four are closely related chemically, the —C H group of carbutamide and tolbutamide being replaced by a —C H group in chlorpropamide and a benzene ring in metahexamide. At the other end of the molecule each has a distinct radical: —NH for carbutamide, —CH for tolbutamide, —Cl for chlorpropamide and 3-amino-4-methylbenzene for metahexamide. In addition, phenylethyl diguanide (DBI, phenformin) has now been released for therapeutic use. This diguanide appears more satisfactory for clinical use than the amyl or iso-amyl derivative. Carbutamide has not been released for use in the United States although it is widely used elsewhere. Possibly its toxic effects—which it must be admitted were seen in only a few patients—resulted from the rather long duration of action of this agent. Tolbutamide has enjoyed a virtual monopoly in this country and has been found surprisingly safe, possibly because it has a half-life of only 6 hours. Optimal effect may require administration of 2-3 doses daily. Chlorpropamide has the longest action of all, with a half-life of about 36 hours, so that the blood level builds up during the first 4-6 days of administration. Metahexamide has a slightly briefer action, with a half-life of about 24 hours; its blood level and hypoglycemic action accumulate for the first 3-4 days. Phenformin has a very brief action, lasting about 5 hours, and optimal control may require that it be given 2-3 times daily. Overdosage of all these agents is capable of producing nausea and vomiting. Experience has shown that the short-acting tolbutamide is effective in doses of 0.5-2 Gm daily, phenformin in doses of about 25 mg 3 times daily, chlorpropamide in doses of 0.1-0.4 Gm daily and metahexamide in doses of 0.1-0.8 Gm daily. In effect the emetic action is a built-in safeguard against overdose. It appears to result from central stimulation and is specifically relieved by administration of dextroamphetamine. The cited doses and durations of action are

Amelioration of Hypercalciuria Following Poliomyelitis by 17 Ethyl 19 Nortestosterone (Nilevar®) is reported by Fred Plum and Marcelle F Dunning[9] (Univ of Washington) Nilevar® had a pronounced effect on the calcium metabolism of 9 extensively paralyzed patients convalescing from anterior poliomyelitis It was given orally in daily dosages approximating 1 mg/kg body weight

The data on urinary calcium excretion during the pretreat

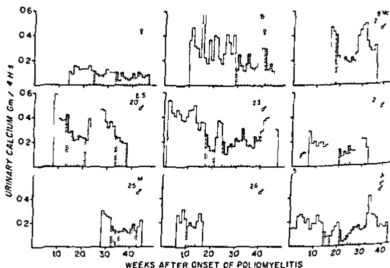


Fig 1—U y l c et d g stud C os h t h g p e t p l d r g wh h h p t nt ec l l mg N lev g/kg body w ght/d (C t y f J l m F a l D n g M F J Cl E d l 18 860 871 A g t 1958)

ment treatment and posttreatment periods are given in Figure 21 Of 9 patients 7 had hypercalciuria at the time treatment was initiated Each patient had a significant (P< 05) or highly significant (P< 01) reduction in daily urinary calcium excretion during treatment As a rule the urinary calcium *fell modestly during the first week of therapy but after* that the mean values averaged 45 4% less than during control periods There was no tendency to escape from the effect of the drug the lowered calcium excretion persisted throughout periods of treatment lasting 3 12 weeks Five patients in

(9) J Cl F l c l 18 860 871 A g t 1958

carbohydrate) from fat could occur in possibly predisposing nutritional and hormonal conditions If certain pathways principally involving ketone bodies as intermediates had been operational then the 1 2 5 and 6 carbons of glucose would have been substantially labeled The findings do not

F g —R t on f m g gl ns f m t t t l to-t l ondensat on t t d den t on w th gly xal t to m l t A t k di t loc t f C (Court y f Sb W W nd Hen A R J Cb I t 37 1006 1015 J l 1958)

exclude all possible reactions that could result in gluconeogenesis from fat

Small amounts of tracer (le s than 2% of the total glucose C^{14}) were present in each of the 1 2 5 and 6 carbons in such proportion as mainly to suggest derivation by reactions of the pentose phosphate cycle In these carbon positions C^{14} was present in about the same pattern and amount as with nondiabetics In labile diabetics with marked ketosis about 4% of the administered C^{14} was estimated to be present in free body glucose 2 hours after injection whereas in stable diabetics with or without glucocorticoid administration about 2% was found in gluco e at this time

of course modified when the organs responsible for the metabolism and excretion of the agents are diseased. For example the effect of tolbutamide is prolonged in diseases of the liver and that of chlorpropamide in renal insufficiency.

Experiments on administration of combinations are just now in process and I are not yet in print. Dolger refers to "unbelievably" good control with combinations of phenformin and tolbutamide particularly in brittle diabetes. That these agents are being tolerated with surprisingly little toxicity is particularly gratifying to those of us who recall the days of Synthalin derived from the earlier Glukhorment devil's club uva ursi blueberry leaf extract oxycatalyst Solanum sanitwongsei berries guanidine intoxication akee Corchorus olitorius aspergillin and so on. Surprisingly little has been reported so far on the efficacy of the tryptophane derivatives such as the naturally occurring 3 indolacetate which Mirsky found effective in the treatment of human diabetes.—Ed

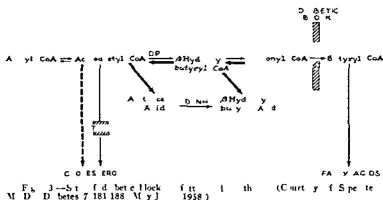
Glucose Metabolism

Pathways of Carbohydrate Formation in Man II Effect of Diabetes and Glucocorticoid Administration on Isotope Distribution in Glucose from Subjects Given 1 C^{14} Acetate Production of glucose in various states of clinical diabetes was investigated in 5 patients by Walton W Shreeve and Allen K Hennes[1] (Brookhaven Nat l Lab Upton N Y). Two were young labile diabetics who were in a condition of marked ketosis and acidosis 1 was a stable diabetic with some clinical evidence of increased adrenal activity and 2 were middle aged obese stable diabetics to whom a large dose of prednisone had been given shortly before the study. Mild ketosis was present in the latter 2.

Intravenous injections with a trace amount of 1 C^{14} acetate were given to each patient followed in 2 hours by collection of blood and in some instances by collection of urine for glucose analysis. Degradation of glucose (by fermentation with Leuconostoc mesenteroides) and analysis of C^{14} content of each carbon position showed 96-98% of the glucose C^{14} in the 3 and 4 carbons as has been previously observed in animals and nondiabetic persons. These findings are consistent with the operation of the tricarboxylic acid cycle and/or fixation of carbon dioxide followed by reversal of glycolytic reactions as the means for appearance of C^{14} in glucose. The occurrence of the conventional glucose labeling pattern fails to provide evidence for utilization of special metabolic pathways by which gluconeogenesis (net gain in

(1) J Cl I v t 37 1006 1015 J ly 1958

this metabolic block coenzyme A derivatives of acetoacetic acid and beta hydroxybutyric acid would be prevented from participating in the further synthesis of fatty acids As shown by the heavy arrows in Figure 23 the concentration of these compounds would as a consequence ri e and their free acids would then accumulate by direct splitting off of coenzyme A



F 3—S t f d bet c block f tt l th (C urt y f S pe te M D D betes 7 181 188 M y J 1958)

or by conversion of free acetoacetic acid to beta hydroxybutyric acid

The author postulates that the metabolic le ions in the Krebs cycle and in protein synthesis observed in the diabetic state may al o be due to deficiency of the coenzyme TPNH

OTHER SUGARS

Hereditary Fructose Intolerance Hitherto Unknown Congenital Metabolic Disturbance Inborn errors of metabolism are due to hereditary lack of certain enzymes or enzyme systems Errors in carbohydrate metabolism include the various forms of glycogen storage disease and galactosemia which are accompanied by severe clinical symptoms and benign asymptomatic melituria An inborn error of fructose metabolism was observed by E R Froesch A Prader A Labhart H W Stuber and H P Wolf[3] (Univ of Zurich) in 4 patient all related

Girl 6½ showed a slightly enlarged liver with normal liver function Glucose and galactose tolerance tests were norm l N tra t e allergy was noted She had developed poorly as an infant be u t

(3) S hw m d W h sch 8 1168 11 1 S pt 14 1

Because nondiabetic persons in corresponding studies showed an average of 1 5% of administered C^{14} in glucose the data are suggestive though by no means conclusive of an increased rate of carbohydrate synthesis from acetate in the labile acidotic diabetics The isotopic data suggest tail to tail condensation of two molecules of acetate to form succinate (Fig 22)

Glycolytic Pathways Their Relation to Synthesis of Cholesterol and Fatty Acids Using liver homogenates of normal and diabetic rats Marvin D Siperstein (Southwestern Med School) studied the relation between the two known pathways of glucose catabolism and the synthesis of lipids It was concluded that in the normal liver the glucose oxidized via the hexose monophosphate shunt may be primarily responsible for the effects of glycolysis in enhancing fatty acid and cholesterol synthesis Evidence indicated that the cofactor mediating these effects of glycolysis is the coenzyme reduced triphosphopyridine nucleotide (TPNH) The study also suggested that cholesterol synthesis in the cell may be controlled by the relative amounts of glucose using each of the glycolytic pathway with hexose monophosphate glycolysis stimulating and Embden Meyerhof glycolysis tending to depress sterol synthesis

The impaired synthesis of fatty acids which is characteristic of diabetes is ascribed primarily to the deficiency in this disease of glycolysis via the hexose monophosphate shunt The data represent the first demonstration that the specific defect in diabetic lipogenesis is probably lack of TPNH normally produced by this pathway The site of the second diabetic block would be at the TPNH dependent conversion of crotonyl coenzyme A to butyryl coenzyme A (Fig 23) The location of the lipogenic lesion of diabetes at this site has an important bearing on several other metabolic abnormalities observed in clinical diabetes Diabetic ketosis is characterized by the appearance of an excess of the ketone bodies acetoacetic acid and beta hydroxybutyric acid It would follow from the author s results that these two acids accumulate in part as a consequence of the lesion at the TPNH dependent step in fatty acid synthesis Because of

(2) Diabetes 7 181 188 May Jun 1958

this metabolic block coenzyme A derivatives of acetoacetic acid and beta hydroxybutyric acid would be prevented from participating in the further synthesis of fatty acids. As shown by the heavy arrows in Figure 23 the concentration of these compounds would as a consequence rise and their free acids would then accumulate by direct splitting off of coenzyme A

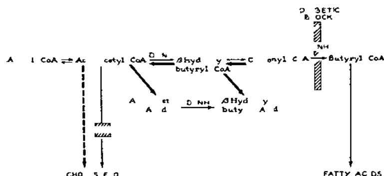


Fig 3—St f d bet block f tt y th (C rt y f S pe t M D Diabet 7 181 1 8 M y J 1958)

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Other Sugars

Hereditary Fructose Intolerance Hitherto Unknown Congenital Metabolic Disturbance Inborn errors of metabolism are due to hereditary lack of certain enzymes or enzyme systems Errors in carbohydrate metabolism include the various forms of glycogen storage disease and galactosemia which are accompanied by severe clinical symptoms and benign asymptomatic melituria An inborn error of fructose metabolism was observed by E R Froesch A Prader A Labhart H W Stuber and H P Wolf[3] (Univ of Zurich) in 4 patients all related

Girl 6½ showed a slightly enlarged liver with normal liver function Glucose and galactose tolerance tests were normal No fructose allergy was noted She had developed poorly as an infant bec u e t

(3) S hw med W h sch 87 1168 11 1 S [t 14 1

frequent vomiting At 6 months the mother had noticed that vomit ing often accompanied by sweating trembling and somnolence fol lowed use of sugar in food The same symptoms were noted later after all sweetened meals and drinks and after ingestion of fruit and carrots Pure glucose and dextrin maltose mixtures were well toler ated Finally aversion was noted against anything sweet and the child developed well only after all foodstuff that she could not tolerate was omitted from the diet

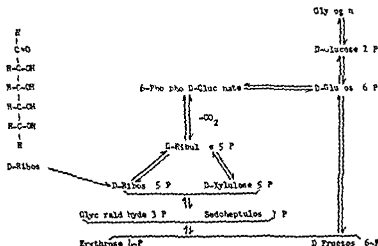
The disorder is distinguished from so called essential fructosuria by occurrence of hypoglycemia and severe symp toms on ingestion of fructose The mode of inheritance is probably of the autosomal recessive type In the authors pa tients administration of fructose led to excessive and pro longed rise in blood fructose levels and to urinary excretion of about 10% of the ingested fructose Concurrently with the rise in blood fructose levels the blood glucose level fell as low as 10 mg/100 ml This severe hypoglycemia lasted several hours and was accompanied by nausea hemorrhagic vomiting trembling profuse sweating and somnolence Aft er cessation of the acute symptoms slight and transient hy perbilirubinemia and albuminuria appeared

The disorder may result from congenital absence of an enzyme responsible for one of the steps of fructose metabo lism by the fructose 1 phosphate triose pathway

Metabolism of D Ribose in Man *was studied by* Stanton Segal and Joseph Foley[4] (Nat l Inst of Health) by infusion of both labeled and unlabeled sugar Twenty seven intrave nous infusions of various amounts of d ribose were given to 6 fasting normal male volunteers and 1 female aged 19 and 24 and to 3 patients with diabetes mellitus All normal subjects were maintained on a 250 Gm carbohydrate diet before the study Diabetics received their last dose of crystal line insulin 24 hours before each experiment The ribose so lution was administered over a 15 minute period or after a small priming dose by constant infusions using a Bowman pump

The pentose was rapidly and extensively metabolized a principal fate being conversion to body glucose via the pentose phosphate pathway (*Fig 24*) *Although converted* to glucose the infused ribose caused lowering of blood glu cose presumably by inhibiting the enzyme phosphoglucomu

(4) J Cl I e t 37 719 3 M 1958



F g 24 —S en f e ct s for ent nc f bose nt pent ph phat p h w d t n n t gl ose (Court y f Serg l S nd F t y J J Cl n I est 37 719 735 M y 1958)

tase thus preventing glycogen breakdown in the liver Ribose was in ulin re ponsive although its response was smaller than that observed with other pentoses

Glucagon

Clinical and Metabolic Effects of Glucagon were analyzed in 8 patients with rheumatoid arthritis and allied disorders by C Ezrin J M Salter M A Ogryzlo and C H Best (Univ of Toronto) Glucagon was administered by slow intravenous drip in doses of 2 5 25 mg /day It was usually dissolved in 500 cc normal saline The infusion was begun 1 hour before breakfast and allowed to run for 10 hours The longest uninterrupted course was 4 days

Prolonged administration of glucagon led to increased urinary excretion of total nitro en and 17 hydroxycorticoids ketosis and decrea ed excretion of creatine Tran ient hyperglycemia always occurred an l sustained elevation of blood sugar levels was usual but less constant Adminis tration of glucagon was followed by temporary relief from acute inflammation in several of the patients Side effects that were

( ) Canad M A J 78 96 98 J 1 1958

noted were extreme nausea hyperglycemia and ketosis

The benefits derived from short term administration of glucagon in the dosage used were not great enough to outweigh the distressing side effects produced The striking metabolic changes observed and their association with reduction in the acute inflammatory process were however of great interest Further experimental study of such changes may lead to better understanding of the mechanism of inflammation

***Effect of 17 Ethyl 19 Nortestosterone on Hyperglycemic* Action of Glucagon in Humans** may assist in elucidating the role of glucagon in the normal body economy Shirley Weisenfeld[6] (State Univ of New York New York City) observed 16 patients aged 41 80, 14 were women 3 of whom were diabetics Eight patients were treated with 17 ethyl 19 nortestosterone (Nilevar®) when the study was instituted and the other 8 were treated with Nilevar® after control glucagon tolerance tests The glucagon tolerance test required *intravenous injection of 0 1 mg crystalline glucagon* The lower limit of normal response is a rise in blood sugar of 20 mg/100 ml Nilevar® uniformly produced a highly significant depression The abolition or suppression of response to glucagon by Nilevar® was reversible when Nilevar® therapy was discontinued Nilevar® had no apparent effect on control of the 3 diabetics nor on the 24 hour thyroid I^{131} uptakes of 8 patients in whom this determination was made

Only a few conditions are known in which human beings fail to respond to intravenous administration of glucagon e g depletion of liver glycogen and enzyme deficiency preventing glycogenolysis as in deficiency of glucose 6 phosphatase in glycogen storage disease The mechanism whereby Nilevar® also blocks this reaction is speculative It might block glucagon induced hyperglycemia by preventing the enhanced gluconeogenesis and protein catabolism However since it has progestational and androgenic activity it may inhibit pituitary and adrenal glucocorticoid secretion perhaps *resulting* in decreased liver glycogen and diminished hyperglycemic response to glucagon It also may be an enzyme poison Actual liver cell damage may be produced

(6) Proc Soc Exp Biol & Med 97 764 767 Apr 1958

although the rapid return to normal glucagon responsiveness after discontinuation of Nilevar argues against this. Moreover, normal I[131] uptakes in patients so studied are indirect evidence of lack of pituitary inhibition. Whatever the mechanism may be, it may provide insight into the role of glucagon.

Effects of Glucagon on Renal Function in Man were evaluated by H. Elrick, E. K. Huffman, C. J. Hlad, Jr., N. Whipple and N. Staub (Univ. of Colorado) with the technical assistance of A. L. Smith and V. Yearwood Drayton. Glucagon caused a significant and sustained increase in the renal clearance ratio of inorganic phosphorus and a significant but transient increase in the renal clearance ratios of sodium chloride and potassium. These effects were significantly different from those observed with glucose, though the magnitude of the hyperglycemia induced by these two substances was not significantly different. Further, in a number of subjects the electrolyte effect after glucagon preceded the rise in the level of blood sugar, suggesting that the effects of glucagon on the renal clearance of electrolytes are not mediated through its hyperglycemic action.

There were no significant alterations in the plasma level of sodium, potassium or chloride after glucagon or glucose. Plasma phosphate concentration decreased after both. However, statistical analysis revealed a greater decrease after glucagon than after glucose.

Most of the changes in creatinine and inulin clearance after administration of glucagon bore no relation to the electrolyte response. Inulin clearance was unchanged and changes in creatinine clearance were of borderline significance. The findings indicate that the increase in electrolyte clearance ratio after glucagon is not due to an increased urine flow. Evidence is presented that these effects of glucagon are not secondary to inhibition of carbonic anhydrase.

Because glucagon markedly increases the excretion of electrolytes but does not change the filtered load appreciably, it appears to have an action on the renal tubule. Since changes in glomerular filtration rate and renal plasma flow were slight, the possibility of an action of glucagon on the glomerulus cannot be ruled out.

( ) J. Clin. Endoc. [illegible] 18:813 [illegible]

Diabetes Mellitus

Main Effects and Interactions of Cortisone Growth Hormone and Triiodothyronine in Production of Temporary Diabetes in Rat were studied by John A Owen Jr and Frank L Engel[8] (Duke Univ) The design of the experiment

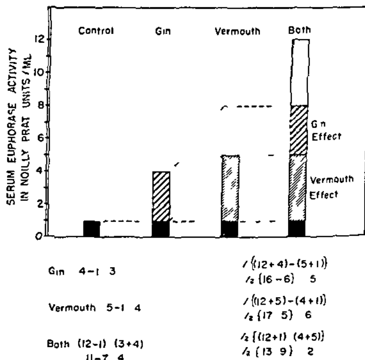


Fig 25—Effect of gin and vermouth on euphorase activity (Courtesy of J A Owen Jr and F L Engel)

was *factorial suitable for the analysis of variance* Intact tube fed albino rats were used

Growth hormone produced hyperglycemia glycosuria nitrogen retention and gain in weight The other hormones produced hyperglycemia and glycosuria with nitrogen wastage and weight loss *Every combination of hormones pro*duced changes in each parameter which were equivalent to the additive effect of the individual hormones No significant

(8) Endocrinology 63 122 131 July 1958

synergistic or antagonistic interactions were demonstrated

Failure to demonstrate any significant interactions was surprising but its implications are meaningful only within the limits of the experimental situation One such limit is the size of the experiment By calculation a significant interaction between growth hormone and cortisone would be theoretically attainable if the number of animals were doubled Even then the values would be minor compared with the main effects Another limit is the duration of the experiment A third consideration arises from the fact that each of the hormones was administered in an unphysiologically large dose in an attempt to produce a prompt metabolic derangement Homeostatic mechanisms would be expected to resist these influences vigorously and might obscure a synergistic action which would be apparent in the reverse situation i e replacement therapy in the hypophysectomized organism Finally studies on the whole animal measure isolated biochemical effects in an admittedly crude and indirect fashion True synergism and competition might best be reserved to describe phenomena occurring at the cellular or subcellular level

Regardless of methodology this experimental design clearly permits more thorough extraction of information from the data It will undoubtedly be of great value in any study which attempts to separate truly synergistic effects of treatment combinations from those which are merely additive

► {*Besides important scientific information this paper offers an experimental design which could be used as a model for studies of so-called synergism In the original presentation at the meeting of the Southern Section of the American Federation for Clinical Research in New Orleans Jan 24 1958 the authors wittily presented the preceding diagram (Fig 25) It is worthy of considerable study—perusal of course not a field project. Actually if the euphorase activity of a martini is greater than that of the control + vermouth + gin the difference must of course be ascribed to the olive I wonder if anyone has studied Gibsons —Ed.*}

Investigation of Symptomless Glycosuria with Galactose and Cortisone Modified Glucose Tolerance Tests was undertaken by R B Goudie W P Stamm and S Dische[9] in 65 patients with history of glycosuria including 5 with clinical diabetes 4 with diagnosis of probable clinical diabetes and 8 referred because of glycosuria but who showed no glycosuria during the test A 50 Gm oral glucose tolerance test was

(9) J Clin Path 11 4 8 436 September 1958

done on each patient with use of capillary blood for true blood glucose estimations of the fasting 1 hour and 2 hour samples The next day a galactose tolerance test was performed according to methods previously described by the authors

Patients were grouped according to glucose tolerance results Patients in groups A and B had clinical or probable clinical diabetes respectively Those in group C showed no clinical symptoms but had pronounced impairment of glucose tolerance with peak blood glucose level over 185 mg and a 2 hour value over 135 mg/100 ml Patients in group D showed mild impairment of glucose tolerance with peak value over 170 and a 2 hour value between 106 and 135 and those in group E showed a peak value over 170 and a 2 hour level of 80 105 Patients in group F showed a peak value over 170 and a 2 hour level under 80 (The curves of patients in groups E and F therefore correspond roughly to the oxyhyperglycemic or lag curves described by other workers The subdivision of these patients with abnormal peak and normal 2 hour values into the two groups is based on the authors observation of the inverse relation of peak and 2 hour levels of blood glucose in normal persons) Patients in group G showed renal glycosuria with peak glucose value under 170 and 2 hour value under 105 and those in group H showed renal glycosuria with peak value under 170 and abnormal 2 hour value of 105 mg or over Patients in group J had had glycosuria but did not demonstrate it at the time of the glucose tolerance test

Comparison of mean galactose peak results with glucose tolerance results showed a highly significant difference between the normal persons and group F similar to that previously reported between normal persons and postgastrectomy patients There was no significant difference between peak galactose values obtained in the normal control and those in any of the other groups

The cortisone modified glucose tolerance test after the technic of Fajans and Conn given to 27 patients with glycosuria and 21 controls was insufficiently sensitive to assess the significance of glycosuria associated with borderline glucose tolerance

With the oral glucose tolerance test presence of a normal

fasting blood glucose level and a high peak associated with a less than normal 2 hour level probably indicates rapid absorption of glucose Confirmatory evidence may be obtained with the galactose tolerance test When the peak is high and the 2 hour glucose level is within normal range but above normal average impairment of glucose tolerance should be suspected especially in presence of normal galactose tolerance

Prediabetic State in Man Definition Interpretation and Implications were presented by Jerome W Conn[1] (Univ of Michigan) in the Banting Memorial Lecture at the meeting of the American Diabetes Association June 21 1958 Previous studies by Conn and his co workers have shown that among apparently normal persons marked differences exist in susceptibility to or resistance to loss of tolerance produced by administration of fairly large doses of cortisone With a cortisone glucose tolerance test an attempt was made to pin point the potential diabetic before the disease is evident by present testing methods

The standard glucose tolerance and cortisone glucose tolerance tests were given to 387 close relatives of diabetics and to 125 persons who knew of no diabetes in their families If the subject weighed under 160 lb 50 mg cortisone acetate was administered orally 8½ and again 2 hours before a standard glucose tolerance test was performed If the total body weight exceeded 160 lb 62 5 mg was given orally on the same time schedule

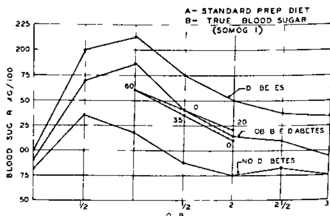
In interpreting the glucose tolerance test a value of 160 mg/100 ml or higher in the first hour 140 mg or higher at 1½ hours and 120 mg or higher at 2 hours is considered indicative of diabetes (Fig 26) A curve under 160 at 1 hour and under 110 at 2 hours is regarded as indicating normal tolerance When the 2 hour value falls between 110 and 120 mg/100 ml it is classified as belonging to a special group designated as probable diabetes

The ordinary glucose tolerance test showed that 18% of the 387 close relatives were already diabetic without knowing it Another 14 (4%) were probably diabetic Of the 125 persons with no known family history of diabetes only 1

(1) Diabetes 7 347 357 Sept Oct 1958

showed a diabetic glucose tolerance test and only 1 had a curve indicating probable diabetes

The persons in both groups who showed normal glucose tolerance curves were then given the cortisone glucose tolerance test as a possible measure of susceptibility to glucose Of 259 nondiabetic relatives 195 (75%) gave a negative re



Fg 6—C te a u d f nt pr t t n f gl t l e te t (Cou t y of Conn J W D b t 7 347 357 S pt Oct 1958)

sponse to the cortisone glucose tolerance test In contrast of 104 persons with no known diabetes in the family 101 (97%) gave a negative response to the corti one glucose tolerance test

Of the 14 persons who were found to be probable diabetics on the basis of the glucose tolerance test 12 (86%) gave a positive response to the cortisone glucose tolerance test The others gave an almost positive response Of 19 patients in whom diabetic glucose tolerance curves reverted to normal after loss of weight 16 (84%) gave a positive response to the cortisone glucose tolerance test

Five year follow up glucose tolerance tests and follow up cortisone glucose tolerance tests were done in 71 relatives of diabetics with normal standard glucose tolerance tests Of the 71 30 had shown a positive cortisone glucose tolerance test Among the 30 positive reactors diabetes or probable diabetes had developed in 23% whereas in only 2% of the

negative reactors had diabetes developed. Of the control group (no family history of diabetes and a normal glucose tolerance test) none retested had shown an abnormal curve.

Finally, very small groups of both positive and negative reactors with family history of diabetes were observed. On repeated testing with the cortisone glucose tolerance test they vacillated between positive and negative responses. This type of instability of carbohydrate metabolism was not noted in any of the persons without family history of diabetes.

Standard Two Hour Oral Glucose Tolerance Test in Diagnosis of Diabetes Mellitus in Subjects without Fasting Hyperglycemia is not an absolutely reliable criterion as is assumed in current practice according to Roger H. Unger (Southwestern Med. School). From a random presumably normal group (applicants for food handler certificates) 152 persons were chosen in whom the blood sugar was less than 130 mg./100 ml. 1½ hours after a meal. They were instructed to eat high carbohydrate diets and to keep diet records with consumption deliberately underestimated for at least 3 days before the tolerance tests which were given in a fasting state.

The fasting blood sugar was less than 100 mg./100 ml. in each case. Values over 100 mg./100 ml. 2 hours after ingestion of 100 Gm. glucose were observed in 83 (54.6%) of the 152 tests. Of these 83 patients 60 had levels at 2 hours exceeding the "diagnostic" 1 hour level of 110 mg./100 ml. Though the antecedent diet was not strictly controlled, the high incidence of "abnormal" values could not be blamed on a low carbohydrate diet since the subjects with the lowest reported intake were not in the "abnormal" group.

Duplicate tests in the same persons under similar circumstances showed wide variations in the same subject at different times. It is therefore unreasonable to base an absolute diagnosis of diabetes on a single test of this kind.

► [The implications of this important study are immediately apparent. If more than 50% of a "normal" population have blood sugar levels exceeding 100 mg./100 ml. 2 hours after a test meal, obviously this test is useless in the diagnosis of diabetes.—Ed.]

Diabetes Following Total Pancreatectomy: Clinical Observations of 10 Cases are reported by E. Perry McCullagh

( ) Ann. Int. Med. 47:1138-1153, Dec., 1957.

James K Cool and Earl K Shirey[3] (Cleveland Clinic) In man and dogs more than 90% of the pancreas must be removed to induce diabetes In normal adults the pancreas weighs 60 160 Gm and may contain between 208 000 and 2 500 000 islets which represent 1 3 5% of the total pancreas Insulin content in a normal person is estimated to be 1 7 units/Gm pancreatic tissue In patients with diabetes this is estimated to be 0 4 unit/Gm The first successful total pancreatectomy was reported in 1942 Since then 29 more cases have been reported All 10 patients in the present series had carcinoma

Insulin requirements immediately postoperatively differ from those in later periods probably because later the food intake is more evenly regulated and absorption differs In the early postoperative period most patients are relatively sensitive to insulin intake of food is irregular and absorption of food is decreased because of diarrhea postoperative stress and absorption of toxic products from the operative site Severe reactions to insulin may even be fatal Some patients require as much as 100 units daily without insulin reaction others show blood sugar fluctuations between normal and as high as 400 mg/100 ml throughout the day with as little as 10 units of insulin

Most patients ultimately require only 10 30 units of insulin daily After total pancreatectomy in a patient with diabetes the daily insulin requirement is not increased and may in fact be decreased In the authors patients after pancreatectomy ideal control implied by the criteria of maintenance of weight and strength avoidance of ketosis and glycosuria and normal range of blood sugar at all times of day could not even be approximated The marked instability of the diabetes judged by extremely rapid variation in blood sugar values was reminiscent of unstable (juvenile) spontaneous diabetes

Caloric absorption after pancreatectomy may be 25 50% below the caloric intake Protein and fat excretion as fecal nitrogen is 2 7 times normal Therefore caloric intake after pancreatectomy should if possible be increased by at least 40% to compensate Pancreatic extract is claimed to aid fat absorption with little effect on protein absorption but there

(3) Diabetes 7 98 30 J l Aug 1958

was no apparent difference in insulin requirements of the pa-
tients who did and did not take it

After total pancreatectomy complete control of diabetes is
difficult to achieve Insulin reactions are prone to be severe
and may be fatal It appears prudent to aim at partial control
of the diabetes and to permit variable degrees of hypergly-
cemia and glycosuria Survival of these patients has been
too short to permit adequate observations about chronic
complications There were no operative deaths but because
of the high incidence of morbidity and early deaths due to the
underlying disease which in no case was cured by total pan-
createctomy this procedure will not be advocated for carci-
noma in the future

Insulitis in Early Juvenile Diabetes according to Ph
M LeCompte[4] (Harvard Med School) who report on in-
fants a boy aged 9 and a young adult may be a clue to the
nature of the injurious agent in human diabetes at least in
the growth onset type These lymphocytic infiltrations of
the islands of Langerhans in the absence of pancreatitis
are apparently specific for diabetes mellitus and are prac-
tically confined to cases of recent onset in children or young
adults Initially described in 1902 they have received scant
attention but may be of considerable pathogenic significance

Boy 9 had sudden onset of symptoms of diabetes with polyuria and
polydipsia He died 25 minutes after hospitalization in a comatose
condition with a blood sugar value of 772 mg /100 ml Three of his
father s siblings had also died of diabetes at age 16 17 and 26

At autopsy the pancreas showed acute diffuse pancreatitis with
necrosis of some large ducts and extensive infiltration of polymorpho-
nuclear leukocytes in the interstitial tissue especially involving inter-
lobular regions In contrast lymphocytic infiltration of about a fourth
of the islands was demonstrated (Fig 27) A few islands showed in-
crease in connective tissue suggesting that lymphocytic infiltration
antedated acute pancreatitis The appearance of the islands varied
Some showed narrow atrophic appearing cell cords generally co-
incidental with involvement by lymphocytes Others approached
normal appearance but most of these showed hydropic change in
beta cells There were rare examples of apparent continuity between
cells of an island and those of adjacent acini

Histologically the lesions of the pancreas in the other
patients were similar to those just described

Lymphocytic infiltration of the islands occurs in cases

recent onset in children and young adults where one might hope to find evidence of the pathogenesis of the disease It is not characteristic of alloxan diabetes nor of the various types *of hormonal diabetes and does not resemble the infiltration* of eosinophils seen in infants of diabetic mothers Histologically it is associated with narrow cords of cells with scanty cytoplasm and deeply stained nuclei which seem to



Fig 7—Exte v filt t on of lymphocyt w th a d a d l d ed ed f m ×400 (C urt y f LeCompt P M A M A A h P th 66 450 457 O t ber 1958)

be chiefly alpha cells These cords of cells may represent rudimentary islands in which after an injury which induced diabetes there is in some way inhibition of beta cell regeneration

► [Lymphocytic *infiltration in hypofunctioning endocrine organs is be*coming almost a general observation It has long been known in the case of the thyroid in which Hashimoto s disease very often leads to myxedema and in the case of the adrenal cortex in which idiopathic Addison s disease supervenes One cannot help wondering if this may not also be the case in idiopathic hypoparathyroidism and other hypofunctional endocrine states Since we are speculating I wonder whether these patients show appropriate *autoimmune phenomena* similar to those *so readily* demonstrated in patients with lymphocytic thyroiditis —Ed]

Complete Remission of Severe Diabetes is reported by Franklin B Peck Jr W R Kirtley and Franklin B Peck Sr[5] (Indianapolis)

Man 41 had no history of diabetes until onset of illness 1 day before admission when he was found unconscious On admission the blood sugar was 1 280 mg /100 ml plasma carbon dioxide 3 mEq Rabinowitch severity index 24 and the patient was in circulatory collapse During the next 12 hours 1 910 units of insulin were administered Subsequently insulin resistance developed that required 200-400 units of insulin daily to maintain normal glycemia After about 10 days in the hospital the patient s responsiveness to insulin suddenly improved and severe hypo lycemia ensued Regulation was then established with 90 units of NPH insulin which was reduced to 30 units daily until about a month later when insulin was entirely discontinued and the blood sugar remained normal

The disappearance of clinical manifestations has not been accompanied by significant weight loss Ordinary glucose tolerance tests show only a slight delay in return to the starting value at the 2d hour There was a slight delay in hypoglycemic response to an intravenous test dose of insulin These constitute the only evidence of any residual abnormality and after 3 years a latent defect is not induced by the cortisone glucose tolerance test of Fajans Conn Until 5 years have elapsed however recovery should be regarded as remission rather than cure

Urinary Excretion of Zinc in Diabetics was studied by G R Constam W Leemann and F Almasy[6] (Univ of Zurich) The amount of zinc was determined in 24 hour urine specimens In 58 nondiabetics aged 6 75 the amount of zinc varied between 37 and 120 μg /100 ml or 39 892 μg /24 hours (average 537) When determinations were made on consecutive days considerable day by day fluctuation in zinc excretion was noted which did not seem to depend on age or sex In 40 diabetics aged 13 80 who had had diabetes for a month to 24 years urinary zinc excretion varied between 23 4 and 582 μg /100 ml or 394 5 845 μg /24 hours with an average of 1 203 and a standard deviation of 914 3 μg /24 hours

The difference between the average zinc loss of diabetics and that of nondiabetics amounted to 866 μg /24 hours which by the T test appeared statistically significant Thus

( ) D t t 93 97 M Ap 19
( ) S hw m 1 W h h 8 11 11 1 1

on the average diabetics excreted more zinc than nondiabetics Zinc excretions of over 2 000 µg/day were observed in 4 patients with severe decompensation of the diabetes One of these patients was in precoma Of 21 diabetics in whom the 24 hour zinc excretion varied between 1 020 and *1 533 µg 16 were poorly controlled Of the other 5 3 showed* considerable albuminuria 1 was recovering from spinal fracture and 1 had severe osteoporosis Among 24 diabetics who were hospitalized because of poor control daily studies showed steadily decreasing zinc excretion in 16 as soon as proper management was begun independent of the type of *management In a pregnant diabetic this* condition did not seem to influence urinary zinc excretion

Whether the increase in urinary zinc elimination in uncontrolled diabetes is the cause or the consequence of the diabetic disorder or just an accompanying symptom remains to be clarified

Complications

Ketosis

Ketogenesis On the basis of his experiments and those of others William C Stadie (Univ of Pennsylvania) concludes that once oxidation of a long chain fatty acid is initiated the entire molecule of that particular fatty acid is completely dissimilated to acetyl coenzyme A This appears to be explained by the type of deacylases found in the liver Only two deacylases have been demonstrated acetoacetyl coenzyme A and acetyl coenzyme A No deacylase for higher fatty acids than carbon-4 have been demonstrated

Once having been activated a fatty acid molecule continues in an activated state until it reaches the 4 or 2 carbon stage This explains the absence of fatty acids containing intermediate numbers of carbons in livers producing large amounts of ketone bodies from the higher fatty acids

Fluid and Electrolyte Therapy of Severe Diabetic Acidosis and Ketosis Study of 29 Episodes (26 Patients) Helen Eastman Martin Kendrick Smith and Mary Lu Wilson[8] (Univ of Southern California) did thorough serum and urine elec

(7) Diabetes 7 173 180 May Ju 1958
(8) Am J Med 24 376 389 M h 1958

trolyte evaluations and in some in tances balance studies in a group of patients with severe acidosis and ketosis In general three types of fluid (hypotonic isotonic and hyper tonic) were used Schedule 1 consisted in 2 L of M/12 so dium lactate and 3 L modified Butler s solution schedule 2 in 2 L of M/6 sodium lactate and 2 3 L of 0 9% saline schedule 3 in 2 L of a combination of 0 75 L of M/6 sodium lactate with 0 25 L of 0 9% saline and 3 L Butler s solu tion Potassium phosphate and potas ium chloride were given in varying amounts All patients received 200 units of regular insulin intravenously every 2 hours until the blood sugar was below 300 mg /100 ml then smaller intramus cular doses were substituted Tonicity of the serum was cal culated from serum sodium and glucose concentrations

Hyperosmolarity of the serum was present in 52% of the patients initially and was still present after 12 hours therapy in 46% emphasizing the need for hypotonic solutions How ever in the presence of shock volume should be restored rap idly with isotonic fluids and if indicated dextran plasma or whole blood There was little difference in the volume of fluid retained when repair solutions of varying tonicity were u ed However when hypertonic fluids were given there was more hyperosmolarity of the serum after 12 hours therapy than with hypotonic fluids and hypernatremia and hyperchlo remia were frequently noted

Blood ketone levels were estimated in 17 patients On ad mission the range was 89 225 mg /100 ml at 12 hours it was 7 168 mg /100 ml The differences shown in Figure 28 in the rate of fall of blood ketone levels appear too small for conclusions to be drawn regarding the effectiveness of ad ministration of glucose fructose or no sugar

Factors influencing the correction of acidosis included the lactate chloride ratio of intravenous fluids (which was con sidered best when over 1) the entry serum chloride level the use of hypertonic solutions use of large loads of 0 9% sodium chloride and the rate of fall of blood ketone level Detailed balance studies in 8 patients were well correlated with e ti mates from other studies of 5 10% body fluid loss and with balances of certain ions The average ranges of intake in the early more acute phases of treatment sh uld be 70 120 ml water/kg 7 10 mEq sodium kg [illegible] mEq chl ride/kg

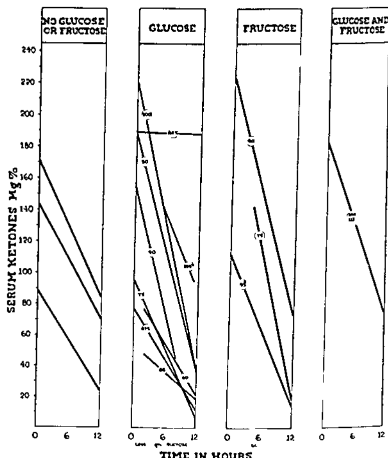


Fig 28—Gl c e a d fru t e th rapy a d rum k t e l l in d abet c k to d Numb r of g m f gl se f t e dm t d d t d b led figu e (Co rt y of M t n H E t al Am J M d 4 376 389 Ma h 1958)

2 3 mEq potassium/kg 0 2 mEq magnesium/kg 1 mM phosphate/kg and 4 5 mEq bicarbonate/kg The authors advocate the following sequence in therapy 2 3 L of a combination of 0 75 L of M/6 sodium lactate and 0 25 L of 0 9% saline followed by 3-4 L modified Butler s solution (containing 57 mEq sodium 50 mEq chloride 25 mEq potassium 21 mEq phosphate 25 mEq lactate and 6 mEq magnesium/L Unless there is a high serum potassium level or

severe oliguria 1 2 Gm potassium chloride is added to the second liter of intravenous fluid and 1 ampule of a special potassium phosphate solution (containing 2 Gm potassium hydrophosphate and 0 4 Gm potassium dihydrophosphate in 5 cc) to the third fourth and fifth liters

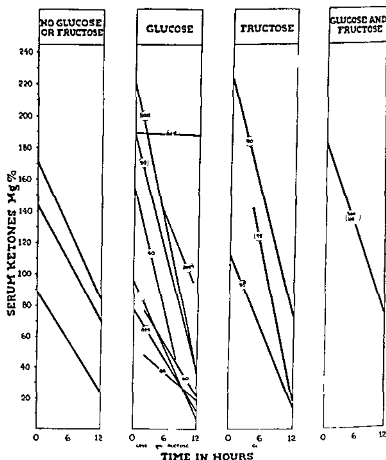
Problem of Increasing Azotemia during Management of Diabetic Acidosis is discussed by Robert W Trever and Leighton E Cluff[9] Most patients with severe diabetic acidosis have some initial nitrogen retention A few display unexplained increasing azotemia during treatment although usually renal function is completely restored eventually

Among 476 adults admitted one or more times in diabetic acidosis to the Johns Hopkins Hospital during 1934 55 in 3 increasing azotemia occurred during management of an episode of acidosis and a ready explanation for the nitrogen retention was not apparent Twenty-one other patients showed persistent azotemia associated with infection or chronic renal disease Although none of the 3 patients had significant oliguria progressive azotemia and the results of urinalyses and kidney function tests indicated impaired renal function These patients may have had acute renal insufficiency secondary to renal ischemia without an evident oliguric phase

Severe Diabetic Acidosis Treated with Artificial Kidney Report of Case Complicated with Acute Renal Failure is presented by Shigeto Aoyama and Willem J Kolff[1] (Cleveland Clinic)

Woman 21 received 7 000 ml saline solution in 18 hours at onset of diabetic coma This corrected dehydration but she received no sodium lactate or bicarbonate to correct the acidosis (serum CO_2 combining power 5 5 mEq /L) This resulted in the strange picture of a patient in severe acidosis and coma but without the usual dehydration The patient might have been saved with conventional methods if the acidosis had been corrected earlier but when seen at the hospital this possibility seemed remote Hemodialysis with the disposable coil kidney reduced the blood urea content from 117 to 48 mg /100 ml in 6½ hours Dialysis corrected the acidosis removed catabolites and permitted further medical management The acute renal failure probably was caused by the combination of hypotension and severe acidosis

(9) Am J M L 24 368 375 M h 19 8
(1) J A M A 166 9 11 J 4 1958



F g 28—Gluco e and f t e th py a d s r m k t e le el d bet k t do s Numb r of g m f gl c fructo dm te ed d t d by c l d fig e (Co rt y f M rtn H E t l Am J M d 24 376 389 M c) 1958)

2 3 mEq potassium/kg 0 2 mEq magnesium/kg 1 mM phosphate/kg and 4 5 mEq bicarbonate/kg The authors advocate the following sequence in therapy 2 3 L of a combination of 0 75 L of M/6 sodium lactate and 0 25 L of 0 9% saline followed by 3-4 L modified Butler s solution (containing 57 mEq sodium 50 mEq chloride 25 mEq potassium 21 mEq phosphate 25 mEq lactate and 6 mEq magnesium/L Unless there is a high serum potassium level or

Fig. 29—R[illegible]lity of [illegible]lar d[illegible] [illegible] 8 a.m. (A) [illegible] 5 p.m. (B) [illegible] by [illegible] by [illegible] (C[illegible] of D[illegible] J[illegible] and C[illegible] D[illegible] R[illegible] Proc. Soc. Exper. Biol. & Med. 97: 4 5 476 February 1958.)

at different times the change was classed as marked. If the calibers differed less than 100% the change was classed as moderate.

Of the 15 diabetics 7 demonstrated caliber changes in the venules within a period of hours. None of 15 healthy comparable control subjects showed such vascular changes. Of the 7 diabetics 3 showed marked and 4 moderate changes (Fig. 29).

With regard to the underlying cause of reversible venular

Mortality of Patients with Diabetic Acidosis in Large City Hospital Thomas G Skillman Rodman Wilson and Harvey C Knowles Jr observed that among 312 cases of diabetic acidosis in the Cincinnati General Hospital during 1947 6 the mortality decreased from 31 4% in the first 5 years to 14 5% in the second

There was no significant differences in the mean ages or degrees of depression of the sensorium of patients in the two groups Nor was there a difference in the incidence of sustained hypotension unresponsive to administration of fluids or plasma expanders The mean concentrations of blood urea nitrogen and serum carbon dioxide content were the same Though the blood glucose concentration was probably decreased by 49 mg/100 ml in the second period ($P<0\,05$) this small difference was not believed to be clinically significant However analysis of nonacidotic complications revealed a significant difference between the two periods During 1947 51 63% of the patients had moderate or severe nonacidotic complications whereas in 1952 56 55% had similar complications Undoubtedly wider use of antibiotics before admission eliminated many of the more serious infectious complications

The lower incidence of nonacidotic complications is suggested as being largely responsible for the decline in mortality Though it could not be shown that altered therapy increased survival in patients without severe complications the use of norepinephrine and parenteral potassium appeared to be lifesaving in some instances

BLOOD VESSELS

Reversibility of Venular Dilatation and Congestion in Diabetic Subjects over a Period of Hours is reported by Jørn Ditzel and Rafael Camerini Davalos[3] (Boston) The conjunctival vascular beds of 15 patients were studied with a stereoscopic microscope (magnification 100) and photographed 2 5 times at irregular intervals between 8 a m and 6 p m The vascular changes were evaluated and graded by measurements *from the enlarged photomicrographs* If the calibers of identical vessel segments differed more than 100 /

( ) D b t 7 109 113 M Ap 19 8
(3) Pr Soc E p B l & M 1 97 4 5-4 6 F b y 1958

liam B Hadley[4] (Harvard Med School) A significant relation was found between the conjunctival pattern abnormality and the extent of small blood vessel degeneration irrespective of the duration of diabetes In general diabetics who exhibited a normal vascular pattern (Fig 30) were those who had the best prognosis with respect to the rate of development of vascular disease Patients who exhibited vascular pattern change I (Fig 31) generally showed rates of pro

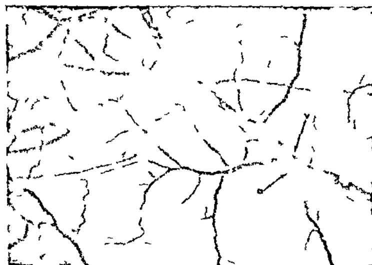


Fig 31—Co j ct l sc l be l f 3 w th li b te for l a h w cul patt n h ge l (rt l |] n l |] d m te ti l) d mod t p g on f d l t la d ed ed f ×48 ((t f D t l J t l AMA Arch I t M d 101 91 9 0 May 1958)

gression of vascular disease between those of patients showing normal vascular patterns and those with vascular pattern change II Young diabetics who showed vascular pattern change II (Fig 32) had a severe prognosis with moderate or rapid progression of vascular disease Patients with the severest venular distention (grade 3) usually had a poorer prognosis than those with less venular distention

The study suggests that abnormal vasomotor changes in the small retinal vessels are important in the development

(4) AMA A h I t M l 101 91 9 0 M 1958

congestion the following observations might be of interest (1) Caliber changes occurred only among the 10 diabetics in whom venular dilatation was present at initial observation (2) In most diabetics exhibiting changes during the day venular dilatation tended to disappear during the later afternoon corresponding to the time at which isophane (NPH) insulin has its maximum effect (3) In diabetics showing vascular alterations the initial observations were made early in the morning thus the presence of more pronounced venular dilatation corresponded to the time when the effect of the isophane (NPH) insulin administered the previous day was minimal No relation was apparent between the venular response change and duration of diabete size of the insulin dose clinical hypoglycemia or actual blood sugar levels

Relationship of Abnormal Vascular Responses to Retinopathy and Nephropathy in Diabetics Study of vascular response patterns observed microscopically in the bulbar conjunctiva was made in 60 young diabetics with retinopathy and nephropathy by Jørn Ditzel Lynn Sargeant and Wil

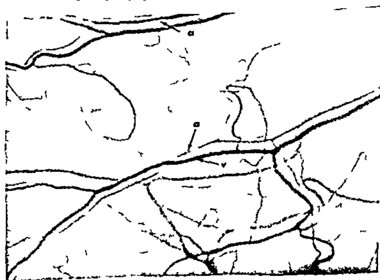


Fig 30 —Con t l v l b d of w m 43 w th d b t f 30 ... h g n l v c l pattern (t l [a] l [ ] d t t l) ... of d b t l d ... e d f m ×48 (C u t y f D t l ... J ... A M A ... h Int M d 101 91 9 0 M y 1958)

were examined about once a month for a period of a year After 90-120 days in diabetic hamsters fusiform distentions of the walls of the veins resulting in sacculations appeared at junctions of veins with larger vessels draining the cheek pouch (Fig. 33) but did not appear on other vessels At least 2 sacculations were present in each cheek pouch



Fig 33—S l t on t en s junct on l d f m ×77 (C rte y f Sud k F \ et l J Cl Endoc 1 6 679 69 M y 1958)

None was found in the controls After 180 days of diabetes distentions appeared in the arterial walls in cheek pouches of 5 of 23 surviving animals together with increase in the number of venous sacculations Two of 6 untreated controls showed a single venous sacculation none was present in the alloxan treated controls One hamster remained diabetic for 370 days and showed 21 venous sacculations and 1 arterial sacculation At this time of 10 controls 7 (including 3 untreated) had 1 5 sacculations The ratio of arteriolar to venular diameters remained constant in all during the experiment In 8 animals that reverted to normoglycemia no lesions appeared to be reversible

Fg 3 —(r t l v ula t d f w m 3 w th d b t fo 17) l w g a cul p tt m h g II (a t l [ ] l [ ] d n te t 1 1) a d p l p f d bet v l d d d f m ×48 (Court y f D t l J A M A A h I t M d 101 912 9 0 M 1958)

of diabetic retinopathy However many other factors undoubtedly play a role

Morphologic Changes in Blood Vessels of Diabetic Hamsters appear to represent acceleration of an aging phenomenon and are comparable to similar changes in blood vessels of the bulbar conjunctiva which have been described in human subjects with diabetes mellitus

Frederick N Sudak Samuel B Beaser Maurice H Shulman and George P Fulton (Boston Univ) found that these changes in hamster cheek pouches increased with the duration of the disease and were irreversible Alloxan was given in diabetogenic dose (60-70 mg /kg for males 70 80 mg /kg for females) to 13 male and 13 female hamsters Alloxan treated nondiabetic animals (that had received only 40 mg /kg alloxan on two occasions a week apart) and untreated animals served as controls No attempt was made to regulate blood sugar levels but insulin was given to sustain the animals and to prevent fatal acidosis Cheek pouches

( ) J Cl E 1 16 679 68 May 1958

Postnatal Weight Loss of Babies Born to Diabetic and Nondiabetic Women The abnormal heaviness of infants born to diabetic women has been ascribed in part to edema. The evidence in favor of the claims that because of this such infants lose more weight postnatally than do normal babies is reviewed by James W. Farquhar and Stanley A. Sklaroff[6] (Univ. of Edinburgh). Because of differences in the criteria of weight loss and in management of the newborn and because of the faulty construction of control groups, this evidence has been found inconclusive.

The weight loss of babies delivered by cesarean section to diabetics has been compared closely with that of babies similarly delivered to nondiabetics and with babies born spontaneously to nondiabetics. When infants of diabetic women are subjected to prolonged fluid deprivation they lose more weight than when fluids are given early and also lose more weight than infants of nondiabetic women by whichever route these have been delivered. Infants of diabetics and nondiabetics delivered by cesarean section lose similar amounts of weight when nursed under similar conditions and also lose more weight over a longer period than infants delivered spontaneously to nondiabetics. They also regain weight more slowly.

Hyperbilirubinemia and ABO Hemolytic Disease in Newborn Infants of Diabetic Mothers Serum bilirubin levels during the neonatal period were studied by R. Zetterstrom, B. Strindberg and R. G. Arnhold (Karolinska Hosp., Stockholm) in 29 newborns of diabetic mothers. The data show that these infants are predisposed to development of hyperbilirubinemia. Average bilirubin levels for the group exceeded those of normal newborns. In most of the infants hemolytic disease or other causes of jaundice could be excluded. Hyperbilirubinemia was considered to be the result of functional immaturity of the liver. Diagnosis of ABO hemolytic disease was made in 5 infants. The high frequency of this complication seems to indicate that development of this disorder is favored in pregnancies complicated by diabetes.

(6) A[illegible] D[illegible] Childhood 33 3 3-329, A[illegible] 1958.
(7) A[illegible] p[illegible] 47 238-250, May, 1958.

TUBERCULOSIS

Tuberculosis and Diabetes *From study of 57 diabetic tuberculous patients* Robert A Scott[8] (State Tuberculosis Hosp Ray Brook N Y) concludes that the mortality rate from pulmonary tuberculosis of diabetic tuberculous patients *who receive adequate chemotherapy should be no greater than that of the nondiabetic tuberculous group* Of 29 patients treated before the advent of chemotherapy 8 (27 5%) were living at the time of the latest examination the rest were dead *Fifteen (51 7%) died of active pulmonary tuberculosis* and 6 of other causes Five of the 6 had active tuberculosis at death The over all mortality from active pulmonary tuberculosis among nondiabetic tuberculous patients who did not receive chemotherapy during the same interval (1936-49) was 6 7%

Of the 28 patients who received chemotherapy 20 (71 4%) were living at the time of latest examination One was considered to have minimal inactive tuberculosis 11 moderately advanced inactive disease and 2 moderately advanced active disease 1 because of persistent cavitation and the other because of failure to finish the prescribed course of chemotherapy Six were believed to have far advanced inactive tuberculosis Of the 8 patients who are dead 4 (14 3%) died of far advanced active pulmonary tuberculosis and 4 of other causes The 4 who died of far advanced active pulmonary tuberculosis had received only short term chemotherapy Of the 4 who died of other causes 3 were considered to have inactive tuberculosis at the time of death whereas the disease in the fourth patient was active Thus in the chemotherapy group 14 3% died of active pulmonary tuberculosis

All deaths from active pulmonary tuberculosis occurred in patients who received chemotherapy for less than 100 days Among patients who received what is now considered to be effective chemotherapy none died because of active pulmonary tuberculosis *In the period covered by the chemotherapy group (1947 56)* 7 4% of the nondiabetics died of pulmonary tuberculosis This included nondiabetic tuberculous patients who received the benefits of chemotherapy as well as some who did not Tuberculous diabetics who re

(8) Am R T 1e 990 998 J 1958

ceived chemotherapy tolerated major thoracic surgery as well as the nondiabetic

HEMOCHROMATOSIS

Diabetes and Hemosiderosis — Hemochromatosis — in Ghana was studied in 50 diabetics by Silas R A Dodu (Accra) Liver function was evaluated by determination of *thymol turbidity bromsulfalein retention and plasma proteins* (total protein and albumin globulin ratio) In 44 instances *sternal marrow suitable for histologic examination* was evaluated for the presence of iron Needle liver biopsies were done in 7 patients showing considerable increase in marrow iron The same 7 patients had skin biopsies

Six patients had elevated bromsulfalein retention accompanied by a reversed albumin globulin ratio Of these only 1 had any increase in marrow iron and this was only a trace However 7 patients (all males) had an excess of histochemically demonstrable iron in the marrow Six successful needle liver biopsies were done on these patients In 5 the amount of histochemically demonstrable iron in the liver was correlated with that in the sternal marrow Four of these patients had cirrhosis all had iron in large amounts in the portal tracts parenchymal cells and Kupffer cells The fifth patient had excessive marrow iron but in the liver the iron pigment was only in the Kupffer cells In the 4 patients with cirrhosis the liver was palpable but bromsulfalein retention was normal despite the demonstrated presence of cirrhosis None of the skin biopsies showed hemosiderin

Thus 6 of 44 diabetics successfully investigated had varying amounts of free iron pigment in the liver 4 had hemochromatosis The incidence would probably have been higher had liver biopsy been considered justifiable in all cases There was a striking lack of agreement between the results of liver function tests and the histologic appearance of the liver in patients with hemochromatosis cirrhosis

Treatment of Hemochromatosis with Chelators With Reference to Three Cases *J Langeron M Paget L Croccel and C Gautier*[1] (Lille) report observations on 3 men aged

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[ ] T R Soc Trop Med & Hyg [ ] 430 September 19[ ]8
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45 49 and 48 who presented different clinical types or at least different stages of hemochromatosis The first had a major form clinically although visceral lesions were not verified anatomically except in the liver The second patient had diabetes cirrhosis pigmentation and sexual impotence Disturbance in glucose metabolism was primary and produced severe acidosis in the initial phase The third patient had hepatomegaly with excess iron but without cirrhosis or diabetes his condition probably represented an early stage of the disease

Ascites which occurred in the first patient is a rare finding in pigmentary cirrhosis and was not accompanied by changes in plasmatic lability or decreased pseudocholinesterase activity Though there was no evidence of hepatic failure and the ascites regressed the patient died about 2 months after its appearance

The endocrine disturbance in these cases aside from diabetes is manifested by sexual impotence Infantilism is occasionally observed Sexual difficulties were definite in the first 2 patients who showed a significant diminution in excretion of 17 ketosteroids These two patients also showed cardiovascular signs The first died in asystole X rays taken 2 months apart showed a generally enlarged heart with severe bilateral stasis The second patient showed ECG changes typical of myocarditis which occurred during an exacerbation of diabetes (an increase of 15 units of insulin being necessary) This suggested that the myocarditis was secondary to metabolic changes rather than to a pigmentary lesion

The chelator used in these cases calcium disodium ethylenediamine tetra acetic acid (EDTA) produced no complication Calcemia was not changed in the second patient and after treatment study of the urine of the third patient showed excretion of 90 mg calcium/day for 1 600 µg iron No tetany was noted but the dose administered never exceeded 0 50 daily by slow perfusion

Effect of treatment was inconsistent It was nil in the first patient but seemed definite in the second patient in whom the first course produced functional improvement durable decrease in pigmentation and a surprising regression of hepatomegaly It is more difficult to evaluate the effect on dia

betes because spontaneous fluctuations occur without apparent cause as *in juvenile diabetes*. *Urinary excretion of iron increased strikingly in the first and second patients. This does not necessarily imply clinical improvement but general well being seemed to accompany this finding.*

As EDTA is not a specific medication in hemochromatosis, possibilities of correcting excess of iron would be limited to cases of intense or chronic deposition of iron. If a significant recovery of iron is accomplished it may not produce any clinical *improvement because of organic changes which* continue to favor deposition of iron.

Chelator drugs act to increase elimination of iron and thus contribute to prevent increase of visceral infiltrations. They are more effective when administered early.

* [The quantitative data on the amount of iron removed are rather disappointing. For practical purposes I believe larger amounts of iron can be removed by phlebotomy.—Ed.]

Oral Hypoglycemic Agents

Aspirin and Diabetes Mellitus appear to have opposite effects on carbohydrate metabolism. A man, 26, who required insulin showed striking amelioration of his diabetes while undergoing salicylate treatment for acute rheumatism. He was able to dispense with insulin for some time and the urine *remained sugar free and the fasting blood sugar was* normal. These findings prompted James Reid, A. I. MacDougall and M. M. Andrews (Western Infirm, Glasgow) to reinvestigate the effect of aspirin in diabetes mellitus using *7 patients besides this young man*. An intensive 2 week course of aspirin abolished glycosuria and lowered the fasting *blood sugar to normal or near normal in these 7 mild to* moderately severe diabetics. There was no decisive effect on glucose tolerance, *although the blood sugar curves* were always lowered during aspirin administration. Moderate ketonuria in 2 patients was reduced to normal with aspirin. Despite the large doses used, serious toxic manifestations were not conspicuous, although tinnitus and deafness were annoying. Four patients tested showed increases in the PMR *during aspirin therapy*.

The reduction in fasting blood sugar in these patients who

(1) B. M. J. 2:1071, Nov. 9, 1957.

were receiving a constant carbohydrate diet coincided with disappearance of glycosuria, indicating that the fall was not due to alteration of the renal thresholds. Absorption of glucose was not impaired. Previously it was observed that a single intravenous injection of sodium salicylate lowers the fasting blood sugar in diabetes. All these factors point to the tissues as the site of action of aspirin.

Earlier literature reports therapy of diabetes with aspirin, but it was abandoned because of serious toxic effects. However, aspirin has an advantage over the sulfonylureas in that serious agranulocytosis is not a problem and there appears to be no danger of hypoglycemia. The actual place of aspirin in the therapy of diabetes mellitus is not apparent, but the problem merits further consideration.

Some Effects of Sodium Salicylate on Muscle Metabolism are reported by K. L. Manchester, P. J. Randle and G. Howard Smith[3] (Univ. of Cambridge). Sodium salicylate, like insulin, increases the uptake of glucose by isolated rat diaphragm and enables the nonutilizable sugar d-xylose to enter the muscle cells. Neither insulin nor sodium salicylate allows free glucose to accumulate within the cells of isolated diaphragm, presumably because the potential rate of glucose utilization within the cell exceeds the rate of entry of glucose into the cell. The effect of insulin on isolated diaphragm differs from that of salicylate in that the latter promotes loss of potassium and diminishes incorporation of C^{14} labeled amino acids into the protein, whereas insulin does not promote potassium loss and increases incorporation of labeled amino acids into protein.

The uptake of glucose into the cells of isolated diaphragm appears to be restrained by an active process dependent on the oxidative production of energy-rich phosphate. It is suggested that salicylate promotes uptake of glucose by inhibiting the production of energy-rich phosphate and that insulin promotes glucose uptake more specifically by limiting the availability of energy-rich phosphate to a process concerned with regulation of the entry of glucose into the cell. The antidiabetic action of salicylate may result at least in part from its effect in increasing the use of glucose by muscle

(3) Brit. M. J. 1:1028-1030, May 3, 1958.

Comparison of Response to Intravenously Administered Sodium Tolbutamide in Mild Diabetic and Nondiabetic Subjects Intravenous sodium tolbutamide response tests were performed in 100 nondiabetics and 79 mild stable diabetics and blood glucose concentration was determined at 20 min

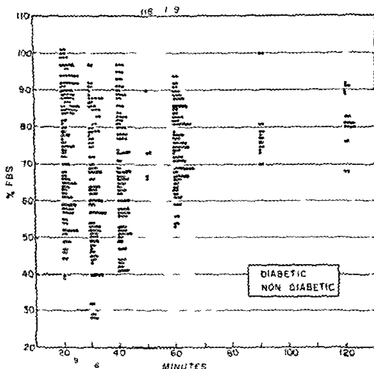


Fig 34.—Tolbutamide response [illegible] of 100 [illegible] d bet [illegible] d 79 mildly diabet [illegible] Blood gl [illegible] 30 m [illegible] (C [illegible] R H [illegible] d Madison L L J Cl [illegible] 37 6 7 30 [illegible] 1958)

ute intervals for up to 2 hours thereafter Roger H Unger and Leonard L Madison[4] (Southwestern Med School) found that whereas the blood glucose levels of nondiabetics fell rapidly reaching a nadir 20-40 minutes after injection diabetics including those with a normal or near normal fasting blood glucose value exhibited a more gradual decline

Figure 34 shows the individual blood glucose levels of all

(4) J Cl [illegible] 37 6 630 [illegible]

diabetics and nondiabetics expressed as per cent of the pretest value *recorded at 20 30 40 60 and in a few instance at 90* and 120 minutes after tolbutamide injection Separation of the two groups is maximal at 20 and 30 minutes at which time the blood glucose level of nondiabetics approaches its nadir Overlap between groups becomes increasingly prevalent thereafter as the blood glucose level of the nondiabetic returns toward its pretest value whereas that of the diabetic continues to decline At 20 minutes after the injection of tolbutamide the blood glucose level of 90% of nondiabetics declined to below 84% of the pretest value and in 94% fell to below 80% of the pretest level In contrast the blood glucose level of 94% of the diabetics remained at 84% of the pretest level or higher and in 95% remained at 80% or more At 30 minutes after the *tolbutamide* injection the *blood glucose* level of 99% of the nondiabetics fell below 77% of the pretest value However in 10% of diabetics declines to 73% of the pretest level or less were noted

*Results of this study accord with the concept that tolbuta*mide enhances the release of insulin from the beta cells If true the more gradual hypoglycemic response to tolbutamide exhibited by diabetics could be ascribed to diminished insulin stores or to decreased rate of insulin release in response to beta cytotrophic stimulation Since there is experimental evidence that tolbutamide potentiates the action of exogenous insulin in totally depancreatized animals results of this study can also be explained on the basis of potentiation by tolbutamide of independently secreted endogenous insulin Validation of either of these hypotheses of sulfonylurea action would provide a rational basis for the observed differences in tolbutamide response In this event response to *intravenous tolbutamide would constitute an index of beta* cell function which might prove useful in diagnosis of mild diabetes

► [This demonstration affords a valuable tool not only for diagnosis but also for the study of insulin production by the pancreas It has been used for this purpose *by Mirsky in the following report* —Ed]

Insulin Producing Capacity of Pancreas in Children with Diabetes Mellitus is evaluated by R Klein J Marks and I A Mirsky[5] (Univ of Pittsburgh) who essay to define the

length of the interval between onset of clinical signs of diabetes and exhaustion of islet tissue using insulin dependent hypoglycemic agents tolbutamide and indole 3 acetic acid Tolbutamide was given orally as 50 mg /kg and indole 3 acetic acid as 2 Gm /sq m body surface The 16 diabetic controls ingested sodium bicarbonate instead The study group included 39 children who were tested within 3 months after diabetes had been diagnosed 33 who had had diabetes 6-24 months 23 who had had it 24-48 months and 25 who had had it 48 months or more The concentration of blood sugar at intervals after ingestion of the insulin dependent compounds was expressed as a percentage of the initial fasting concentration

Tolbutamide administration resulted in a decrease of blood sugar in nondiabetic children to a concentration of 56 ± 5.8 % of the initial concentration within 30 minutes Nondiabetic children given indole 3 acetic acid showed no significant changes in the blood sugar The 16 diabetic children given sodium bicarbonate had no significant changes in blood sugar Administration of either tolbutamide or indole 3 acetic acid to the new diabetics resulted in a marked hypoglycemic response to about 70 of the initial concentration of blood sugar In children ill 6-24 months indole 3 acetic acid also produced a significant response but tolbutamide did not The over all decrease in the groups with diabetes for more than 2 years was not significantly different from that in the controls

Statistical evaluation of the influence of age at which diagnosis of diabetes was made dosage of insulin initial concentration of blood sugar and duration of the diabetic state on the hypoglycemic response to the two agents showed that the duration of the metabolic disorder was the only variable which was significantly correlated with the hypoglycemic response This was confirmed by sequential testing of the new diabetics for about a year after the first studies for they showed progressively diminishing responsiveness

It is postulated that the pancreas is capable of secreting insulin early in the course of juvenile diabetes but that the ability is gradually and steadily lost so that children with diabetes for over 2 years are almost uniformly unresponsive to these two hypoglycemic agents

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(5) Pediatrics 22 96 August 1958

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Comparison of Effects of Insulin and Orinase[7] (Tolbutamide) on Peripheral Glucose Utilization in Dog Leonard L Madison and Roger H Unger[6] (Southwestern Med School) found that intravenous use of glucagon free insulin (0.7 units/kg) to 9 dogs was followed by marked variability in the degree of the hypoglycemia that ensued and in the magnitude of increase in peripheral glucose utilization as evidenced by change in arteriovenous glucose difference and the arteriovenous glucose difference to arterial blood glucose ratio Sodium tolbutamide (30 60 mg/kg) given intravenously to the same dogs produced changes in this ratio that were remarkably similar to those evoked by insulin in the same dogs The only difference between the action of the two drugs is that increase in the ratio after insulin occurred earlier and was of smaller magnitude

In view of other experimental evidence showing no effect of the sulfonylureas on blood glucose concentration or peripheral glucose utilization in absence of the beta cells of the pancreas these data support but do not prove the thesis that one of the major physiologic effects of tolbutamide is stimulation of endogenous insulin secretion

Secondary Resistance in Oral Treatment of Diabetes Oral antidiabetic drugs have been used in active therapy for over 2 years The types in use are BZ 55 and D 860 The latter is more widely used because of its lower toxicity and because it is not a sulfonamide Gerhard Dotevall (Varberg Sweden) treated 65 diabetics with BZ 55 or D 860 Secondary resistance occurred in 15 after an observation period of 2 18 months Secondary resistance means that patients who have responded well to oral antidiabetic medication for 2 months or more become resistant to the drug This resistance appeared mainly *in the first 6 months and particularly* in patients previously treated with insulin Nine had had insulin treatment earlier Most patients with secondary resistance did not require a larger quantity of insulin after discontinuing oral treatment than before commencing it The mean duration of the diabetes was 6 7 years in patients with secondary resistance and 2 5 years in the other

(6) Met 1 1 m 7 77 39 M 1958
(7) At mel s d v 161 51 56 19 8

It is suggested that secondary resistance is due to a reversible collapse of the beta cells in the pancreas

► [Although the mechanism of action of the oral hypoglycemic agents is still controversial most investigators believe that the two drugs referred to in this article act by forcing the diseased pancreas to increase its output of insulin Since the introduction of these compounds fear has grown on theoretical grounds that they might convert mild diabetes to severe diabetes by whipping the tired horse Actually secondary resistance has occurred rather infrequently and the data are not yet adequate to indicate whether the incidence in patients treated in this manner exceeds that in diabetics who have not been given hypoglycemic agents —Ed]

Teratogenic Effect of Hypoglycemic Sulfonamide (N Sulfanilyl N Butylurie BZ 55) was studied in white rats by R De Meyer and M Isaac Mathy[8] (*Louvain Belgium*) In the strain of rats used trypan blue vitamin A in large doses cortisone and insulin had not produced congenital malformations The sulfonamide was administered to gravid rats by gastric intubation in a solution of 200 mg /cc 500 mg daily for 1 2 or 3 consecutive days Time of administration varied in different groups from the 6th or 9th to the 13th and 14th days of gestation The rats were killed on the 20th day and the embryos fixed in Bouin Allen solution Several were prepared in serial sections of 7 μ

In some animals N sulfanilyl N butylurie BZ 55 caused partial or total absorption of the embryos a rare phenomenon in untreated rats Absorptions seemed more frequent when the agent was administered early in gestation and in high dosage Of embryos living on the 20th day all examined microscopically presented anomalies Microscopic examination of the head showed many instances of persistence of the palatine cleft in controls this was completely closed at this developmental stage Total absence of eyes with persistence of ocular adnexa (lids lacrimal glands and muscles) was frequent In some cases the eyes were in place and the retina presented the usual stratified appearance a small depression indicating the location of the papilla But there was no nerve filament at this point and no artery entered the eye through the papilla In the irises of these abnormal eyes some nerve filaments emerged which apparently were lost in the surroundings of the ocular globe Anophthalmic embryo and those with abnormal eyes did not retain the optic nerve for some fibers were lost on emerging from the diencephalon

(8) A d.c 1 19 167 17 F b 59

No anomalies were found in the pancreas liver lungs kidneys and testes although the last seemed to be poor in seminiferous tubules and germ cells

Anomalies obtained with this sulfonamide partially resemble those produced by pantothenic acid deficiency which results in similar anophthalmia Persistence of the palatine cleft however is not part of the syndrome of pantothenic acid deficiency That the artificial hypoglycemia produced by the drug is responsible for these embryonic changes seems unlikely since large doses of insulin have never produced similar lesions Administration of other sulfonamides for 2 3 days has not produced similar anomalies which suggests that the effect is not due to the sulfonamide radical Abnormal emergence of nerve filaments in the iris is comparable to results which have been reported in grafting of eye The ocular anomaly appears to be regressive Examination of 13 day embryos of rats which had received a daily dose of 500 mg N sulfanilyl N butylurie BZ 55 on the 10th and 11th days showed optic evagination forming normally in the diencephalon Hence atrophy of the optic nerve appears to be a regressive phenomenon and the ocular globe is deprived of its nerve attachment as is a grafted globe

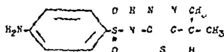
Management of Diabetes Mellitus with Chlorpropamide Preliminary Report is presented by Samuel J N Sugar Lawrence J Thomas and Serkis Tatlier[9] (George Washington Univ) Of 45 patients treated with chlorpropamide a new oral hypoglycemic agent (Fig 35) 26 (58%) showed adequate control Diabetic patients who were taking insulin those inadequately controlled with tolbutamide and an occasional patient who had voluntarily discontinued all treatment for over a year were used in the study

Chlorpropamide was made available in 0 5 Gm uncoated tablets Most patients were started on 1 Gm /day in 2 doses given before breakfast and supper If this proved ineffective 1 5 Gm was given No patients benefited by increasing the dose to 2 Gm /day The dose was decreased usually by decrements of 0 25 Gm when good control as manifested by lowered fasting blood sugar levels and negative urine test was noted Several patients were satisfactorily managed on

(9) M A D st t of C l mb 7 445 450 S pt ml 1958

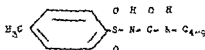
0 25 Gm (½ tablet)/day Most patients required between 0 5 and 1 Gm daily Follow up lasted 3 14 week

Of particular significance was the good response of 16 of 24 patients (67%) who had shown increasing lo of control on tolbutamide Another noteworthy feature in patients clas ified as tolbutamide secondary failures was good re pon e



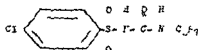
p-aminob nzolsulfonamide isopropylthio azole

(IPTD)



1 butyl-3-p-tolyl ulforylurea

(Orinase tolbutamid)



N Propyl N (p chlo obe enes lfonyl) u ea

(Di binese chlorpropamid)

F g 35 St t al f m l f h pogly If m d l ts (C urt f S k S J N t l M An D a t t C l nl 44 4 S ptembe 19 8)

to a econd cour e of tolbutamide after chlorpropamide was stopped because of side effects Two patients who had been taking insulin for over 3 years remained well controlled after chlorpropamide was discontinued

Toxicity to chlorpropamide was not serious Hypoglycemic symptoms and weakness were prominent ide effects Probably they could be avoided by starting with small doses and working up to an effective level Unstable diabetics of any age are poor candidate for control with chlorpropamide

Clinical Use of Biguanides and Their Role in Stabilizing Juvenile Type Diabetes Attempts to modify the course of juvenile diabetes or to stabilize the action of insulin appear justifiable because of the present natural course of diabetes in childhood After an acute onset often in severe ketoacidosis and after a temporary remission phase in some cases intensification of diabetes occurs By the 5th year of illness about 95% of patients manifest a total disease at which time the insulin requirement has risen to an average of 0 5 unit/lb body weight Control is difficult and complications are ominous

Leo P Krall Priscilla White and Robert F Bradley[1] (Joslin Clinic Boston) report their experience with biguanides in 72 patients with growth onset diabetes The blood sugar was successfully lowered in 64 patients (89%) but of these 29 discontinued the drug because of inability to tolerate the side effects In severe growth onset diabetes it is best to administer biguanides by substituting a combination of DBI and insulin after the patient has achieved maximum control with insulin The insulin is gradually decreased while the DBI is increased until the maximum tolerated DBI and lowest possible insulin dose are reached Insulin in smaller doses is presently being given to about half the patients who remained on biguanides

The best results were achieved in patients with diabetes of short duration The absence of severe hypoglycemic reactions was striking Linear growth was satisfactory in all instances Although toxicity was not demonstrated in liver function tests urinalyses or hematologic studies side effects were numerous These included anorexia nausea vomiting diarrhea and lassitude These effects usually appear 24-48 hours after inception of treatment and subside in 24 hours if the drug is discontinued

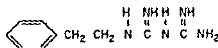
The biguanides are not as facile or as versatile as insulin Their mode of action is not known but their clinical effect appears to be that of reinforcement or potentiation of exogenous or endogenous insulin Activity begins several hours after ingestion and disappears in 6 8 hours making multiple doses necessary

Patients with short term cases who were treated with

(1) D let 7 468 4 7 N D 1958

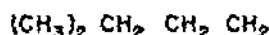
biguanide alone appeared to have done better than expected in delaying natural intensification of diabetes. Those with long term cases did better than expected in respect to insulin requirement. Biguanides appear to be useful adjuncts in the total therapy of juvenile diabetes if the side effects can be tolerated or eliminated.

Hypoglycemic Actions of Phenethyl, Amyl and Isoamyl Diguanide appeared to be the results of two mechanisms: promotion of anaerobic glycolysis with increased glucose





AMYL-



ISOAMYL-

Fig 36 (C rt y f W ll m R H r J D bet 7 87 9 M Ap 19 8)

utilization and decrease of gluconeogenesis with a decrease in the output of glucose from the liver in studies reported by Robert H Williams, Donald C Tanner and William D Odell (Univ of Washington). Phenethyldiguanide (PEDG, also designated as DBI, phenylethylformamidinyliminourea and phenformin) (Fig 36) was shown to decrease gluconeogenesis in guinea pigs. This was not considered to be its only mechanism of action in producing hypoglycemia however since in PEDG treated hepatectomized guinea pigs it produced a much greater hypoglycemia than that found in untreated hepatectomized animals. In guinea pigs treated with PEDG (20 mg/kg) the respiratory quotient was increased. Other studies confirm that PEDG causes increased anaerobic glycolysis. Presumably the isoamyl and amyl derivatives act similarly. No toxicity was discerned in guinea pigs given 10 mg/kg PEDG twice daily for 5½ weeks.

(2) Diabet 7 87 9 M Ap 1 8

Clinically the authors found that the diguanides are more effective than tolbutamide in juvenile diabetes They appeared to be particularly useful in brittle diabetes Side effects (especially nausea and vomiting) occurred in over half the patients given full therapeutic doses but subsided promptly with cessation of therapy Isoamyl diguanide appeared less satisfactory than the other diguanides

Insulin

Current Views on Insulin Action According to William C Stadie[3] (Univ of Pennsylvania) the mechanism of action in muscle may be considered to be a combination of insulin with the muscle and the site of the action perhaps on cell surfaces The main metabolic effects would be increase of glucose transport which would accelerate phosphorylation and therefore further reaction

In the liver adaptation is necessary time is required the enzyme systems are under the control of pituitary factor and the chief metabolic reactions involved are glucose oxidation fatty acid synthesis oxidative phosphorylation and perhaps others In adipose tissue the situation is about the same as that outlined for the liver In the brain as many experimenters have found there is no demonstrable action of insulin In other tissues the data available on insulin action are insufficient to make discussion profitable

Action of Insulin on Release of Fatty Acids from Tissue Stores The mechanism by which carbohydrate utilization reduces the concentration of nonesterified fatty acids in the plasma of rabbits and dogs was studied by Edwin L Bierman Irving L Schwartz and Vincent P Dole[4] (Rockefeller Inst) by comparing the clearance of C^{14} labeled palmitic acid before and after administration of insulin

The rate of disappearance from blood of a single injection of C^{14} labeled palmitic acid was identical before and after an intravenous injection of insulin (0 1 unit/kg) although the expected significant fall in total nonesterified fatty acid concentration occurred When a steady concentration of labeled nonesterified fatty acids was maintained by constant

(3) T & St d C ll Phy Ph l d lph a 25 131 141 F l rua y 19 8
(4) Am J Phy l 191 359 36 N mbe 19 7

infusion the administration of insulin significantly increased the specific activity It is concluded that insulin decreases the release of fatty acid from tissue stores but does not accelerate their removal from blood

Studies on Rat Adipose Tissue in Vitro I Effects of Insulin on Metabolism of Glucose Pyruvate and Acetate Albert I Winegrad and Albert E Renold (Harvard Med School) reinvestigated the effects of insulin in vitro on rat adipose tissue by using paired epididymal fat pads with minimal handling of the tissues before incubation

Insulin greatly enhanced glucose uptake oxidation of glucose carbon to carbon dioxide and incorporation of glucose carbon into ether soluble lipid The e effects were apparent within 15 minutes of incubation and were maintained for as long as 6 hours Tissues from alloxan-diabetic animals metabolized much less glucose to carbon dioxide or lipid than did tissues from normal animals but an insulin effect was present on each of these after 3 hours incubation Insulin added in vitro did not significantly stimulate the metabolism of acetate 1 C^{14} or pyruvate 2 C^{14} to carbon dioxide or lipid when these substrates were present alone In the presence of glucose insulin stimulated lipogenesis from acetate or pyruvate

The magnitude and reproducibility of insulin effects on lipogenesis from glucose by adipose tissue suggest that adipose tissue is a major anatomic site of insulin action

Special Aspect of Insulin Resistance in Diabetes Mellitus Antibody Factor was studied by E Cugudda and E Dipen a[6] (Univ of Siena) in rabbits and in 23 diabetics treated with insulin 6 previously untreated diabetics and 10 normal control

Studies were made on hemoagglutination and hemolysis with use of insulin antiserum In 8 patients no evidence was noted in the circulation of antibodies for insulin though some had received 65 units daily for 10 years In 11 diabetic patients agglutination titer was exceedingly low in 3 1 3 in 3 1 8 in 1 1 12 and in 4 1 16-1 32 Value below 1 16 are not a sure indication that antibodies to insulin are pres

(5 J Biol Chem 33 67 August 19 8
(6 Mi rva med. 49 3159 3164 A g 18 19 8

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(3) Tr. & St. d. Coll. Phy. n. Philadelph. 5 133 143 Feb. a. y. 19 8
(4) Am. J. Phy. 1 191 359 36 N. be. 195

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(5) J B l Chem 233 67 72 August 1958
(6) Minerva med 49 3159 3164 Aug 18 1958

ent Among 11 patients hemoagglutination repeated after incubation with *insulin was reduced in 2 (from 1 12 to 1 3* and from 1 32 to 1 4) and disappeared in 9

In 4 patients with diabetes hemoagglutination in immune serum results were definitely positive 1 28 in 1 1 64 in 1 and 1 40 in 2 After incubation with insulin agglutination decreased to 1 8 1 4 1 5 and 0 The 2 with the lower titers received 80 units of insulin daily and the 2 with a titer of 1 40 *85 and 120 units*

In the controls and diabetics not treated with insulin there was no evidence of circulating antibodies to insulin

Results of tests for hemolysis in the three groups were on the whole parallel to those for hemoagglutination There was one instance of hemolysis to immune serum inhibited by preincubation with insulin No significant electrophoretic changes *in gamma globulins were observed* but there was often an increase in the alpha and beta globulin fractions

INSULOMA

Hormone Producing Insuloma in Diabetes Mellitus was observed by Jens Haarstad[7] (Oslo)

Man 75 was treated with insulin for 3 years during which time he was hospitalized for diabetes ulcers and threatened gangrene For 10 years he had shown gradually increasing symptoms of cardiac failure due to arteriosclerotic heart disease At final admission edema difficulty in micturition and signs of uremia were present but the diabetes showed no change and was treated as it had been for some time He had proteinuria without glucosuria or ketonuria Blood sugar was 91 mg /100 ml blood urea 263 mg /100 ml alkali reserve 30 9 vol % and sedimentation rate 129 mm Constantly low blood sugar levels during the first 24 hours led to withdrawal of insulin despite which the level dropped to 31 mg /100 ml with *coma* and cramps The condition was temporarily relieved by intravenous glucose Repeated hypertonic glucose injections given intravenously were required during the next 6 days Increasing uremia and ultimately *anuria led to death at this time*

Hydrothorax and ascites were found at autopsy The heart was hypertrophic with calcified valves and atheromatosis The kidneys were large and pale throughout The surface of the firm enlarged pancreas was unevenly yellow the cut surface was brown with many nodules No evidence of metastasis was seen and the ducts were not obstructed Histologically the interstitial connective tissue was prominent There were several large isolated nodes of cells resembling or

(7) Acta med scand 159 47 49 195

dinary islands of Langerhans. The cells of the adenoma grew in trings and alveoli. Individual cells were cuboid or polyhedral, some what lighter and more acidophilic than usual and had a variable chro matin content. No mitoses or nuclear abnormalities were observed.

The multicentric islet cell adenoma was more extensive than the short duration of the symptoms of hyperinsulinism would lead one to expect. The neoplasms had probably been developing for some time, becoming active in hormone pro duction only during the last days of the patient's life.

Amelioration of Diabetes Mellitus by Insulinoma is ex ceedingly rare. Robert D. Cutler, Gary Zucker, Robert Ei singer and Norman Stoller (Beth Israel Hosp., New York) report such a case complicated by the coexistence of diffuse liver disease.

Man 67 was admitted in November 1956 because of hemorrhage from a colostomy stoma. Polyuria, polydipsia, weight loss, hypergly cemia (to 25_ mg./100 ml.) and persistent glycosuria began in 1945. Severe restriction of carbohydrate ameliorated the symptoms. An adenocarcinoma of the rectum was excised 3 years later. In March 1954 headache, dizziness, aggressiveness, hostility and self-destruc tive urges began. On hospitalization 4 months later the fasting blood sugar was 70 mg./100 ml. A subsequent admission in November 1955 showed a fasting blood sugar of 77 mg./100 ml. and a 2 hour post prandial value of 107 mg./100 ml. No liver abnormality was demon strable. Ascites developed in December 1955. Jaundice, abnormal liver function tests, an alkaline phosphatase of 11.8 Bodansky units and cirrhosis were demonstrated at that time. He also had periodic gastrointestinal bleeding related to the colostomy. Blood sugars were consistently low on all admissions, finally dropping to 35-30 mg./100 ml. in November 1956. At that time glucose tolerance tests, with and without high calorie loading, showed initial fasting hypoglycemia with an abnormally high peak followed by sustained hypoglycemia. An epinephrine tolerance test demonstrated a 4 rise of blood sugar between 3 and 45 minutes. This suggested the existence of adequate stores of hepatic glycogen, a more likely finding in organic hyperin sulinism than in diffuse liver disease. Intravenous administration of 1 Gm. sodium tolbutamide produced a 64% depression of blood sugar at the end of 45 minutes. Laparotomy was performed and a large brownish red tumor at the inferior border at the tail of the pancreas was removed. Hyperglycemia occurred promptly after the operation. Microscopically the tumor was shown to be an islet cell tumor.

The glucose tolerance test did not clearly establish the diagnosis of hepatogenic hypoglycemia in this patient because of the history of pre-existing diabetes mellitus. It was possible that the islet tissue was not only functionally im

(8) New England J. Med. 258:9 91, May 8, 1958.

paired by an insulinoma but also actually unable to respond because of the pre existent diabetic defect Assay of the islet cell tumor showed an insulin content not significantly different from that of normal pancreas This perhaps can be explained by the presence of considerable necrosis or hemorrhage or the turnover rate of insulin production and release may have been exceedingly high

Islet Cell Tumors of Pancreas Producing Hypoglycemia Samuel F Marshall[9] (Lahey Clinic) reports 19 cases of hyperinsulinism caused by functioning islet cell tumor Eight neoplasms were benign adenomas 2 were frank carcinomas and 9 were questionably malignant or of low grade malignancy Most of these islet cell tumors are single—in only 2 cases were there multiple tumors The tumors are usually 1 2 cm in size Those smaller than 5 mm rarely produce hyperinsulinism Seven tumors were in the body of the pancreas 5 in the tail 6 in the head and 1 extrapancreatic in the gastrosplenic omentum The tumors are firmer than surrounding normal pancreas and because of the rich capillary network they are pink They are round firm discrete and usually encapsulated

Symptoms depend on the excess secretion of insulin with resulting hypoglycemia Attacks of hypoglycemia are usually precipitated by fasting or by overexertion and often begin with a feeling of intense hunger The patient may be agitated perspire easily and exhibit pallor dizziness and weakness which may progress to confusion stupor excitement disorientation drunken behavior delirium mania tonic and clonic spasms convulsions and coma Frequently cases are misdiagnosed as epilepsy *alcoholism or brain* tumor and patients are often thought to be psychotic

Before the diagnosis of hyperfunctioning islet cell tumor is made the following criteria must be met (1) symptoms must be severe enough to cause loss of consciousness or at least stupor *(2) symptoms must recur despite adequate* dietary regulation (3) blood sugar must be below 50 mg during an attack (4) symptoms must be relieved by food or sugar (5) organic disease that is outside the pancreas and that is capable of producing hypoglycemia must be excluded

(9) S Cl N rth Am rica 38 775 54 J 1958

and (6) self-administration of insulin must be excluded.

Once diagnosis is established, surgical exploration is indicated. Delay may permit mental deterioration caused by repeated attacks of hypoglycemia. A high protein diet with maintenance of normal potassium and phosphate concentrations is important. If the tumor cannot be definitely demonstrated after careful inspection and palpation, aberrant pancreatic tissue should be sought before radical subtotal pancreatectomy is undertaken. Enucleation should not be done except for tumors in the head of the pancreas. In the other locations partial resection is easily performed. In certain patients in whom a definite tumor cannot be palpated, the surgeon is justified in resecting the tail and body of the pancreas up to the superior mesenteric vessels. About 60% of such patients will achieve relief from symptoms.

In general, surgical results are excellent. Of the 19 cases, 17 were cured. One patient with frank carcinoma is still well 1½ years after operation and 1 patient with carcinoma died subsequently of an unrelated carcinoma of the breast. One patient died postoperatively, a mortality of 4.2%. One patient had recurrence of hypoglycemia and was subsequently cured by more radical operation.

Prolonged Glucagon Administration in Case of Hyperinsulinism Due to Disseminated Islet Cell Carcinoma is reported by Bernard R. Landau, Herbert J. Levine and Roy Hertz[1] (Nat'l Inst. of Health).

In woman, 28, operation established tissue diagnosis of islet cell carcinoma of the pancreas. The primary tumor, an irregular mass in the body of the pancreas, was not removed because of her poor condition. The postoperative course was complicated by hypoglycemia. Two weeks later partial pancreatectomy and splenectomy were performed but neither degree of hypoglycemia nor frequency of attacks was altered despite administration of 27 Gm. glucose hourly. Glucagon, 8 mg. intravenously over 3 hours, produced a rise in blood sugar from 50 to 175 mg./100 ml. but hypoglycemia recurred rapidly on its discontinuance. Glucagon, averaging 13 mg. daily, was given in continuous intravenous glucose infusions for 33 days. During the first month the attacks were reduced and glucose requirement averaged only 14 Gm. hourly, but subsequently rose. After each of 6 tests in withdrawal of glucagon only, the blood sugar level fell and in 3 tests hypoglycemic episodes occurred. Glucagon was discontinued after 72 hrs. For the next 5 days hypoglycemic episodes were not prevented

(1) New England J. Med. 59:86-88, Aug. 7, 1958.

by hourly administration of 38 Gm glucose Glucagon reinstitution resulted in fewer hypoglycemic episodes but the glucose requirement was 35 Gm/hour On the 88th day the patient died Autopsy showed lung congestion extensive liver metastases and intestinal obstruction due to tumor at the splenic flexure

The observation of elevated blood sugar levels for 8 hours during an initial glucagon response test may indicate large glycogen stores derived from large amounts of gluco e and insulin The ability of glucagon to maintain an elevated blood sugar level for 55 days in this patient does not seem explainable by this mechanism because this would require almost 2 months to deplete completely the liver glycogen Another explanation may be that as a result of phosphorylase activation the liver glycogen stores were depleted over a relatively short period and that glucagon showed a continued effect because on its discontinuance glycogen stores were resynthesized from glucose and endogenous insulin Deposition of glucose in the liver would then result in hypoglycemia

Continued glucagon administration could simply prevent liver glycogen depo ition In that case no decrease in glucose requirements should have been apparent except for the initial brief release of the liver glycogen stores This patient s glucose requirement could be estimated by her intake With glucagon this requirement appeared to decrease and hypoglycemic episodes were le s frequent These observations suggest that glucagon may have stimulated production or decreased utilization of glucose by another mechani m

Islet Cell Tumor and Syndrome of Refractory Watery Diarrhea and Hypokalemia John V Verner and Ashton B Morrison" (Duke Univ) report 2 cases and review 7 from the literature to emphasize the frequency with which diarrhea may be associated with noninsulin secreting islet cell tumors of the pancreas

The explosive watery diarrhea was the most difficult clinical problem in the authors 2 patients Short lived improvement occurred in 1 after hydration and electrolyte replacement However both patients died and on autopsy vacuolar nephropathy associated with noninsulin secreting islet cell adenomas of the pancreas were found

( ) Am J M d 374 380 S pt mb r 1958

In none of the 9 patients was a satisfactory clinical explanation of the diarrhea found. Severe hypokalemia was well documented and persistent in 3. The severity of potassium depletion was reflected by vacuolar changes in the renal tubules. The constant fixed low specific gravity of the urine noted in the authors' 2 patients was a characteristic finding of hypokalemic nephropathy.

It is known that prolonged diarrhea may cause potassium deficiency and such a mechanism could well explain the hypokalemia in these patients. The possibility of a substance elaborated by the islet tumor cells being more directly involved in causing the diarrhea or hypokalemia cannot be excluded. The watery nature of the diarrhea is perhaps more compatible with increased production than malabsorption of gastrointestinal juice.

Tetany and edema occurred in 2 patients in association with hypopotassemia and hypercalcemia. There was no evidence clinically or pathologically of hyperinsulinism or peptic ulceration in the authors' 2 patients and no parathyroid adenomas were found. In only 1 of the 9 patients was resection of islet cell tumor carried out early enough to cause the symptoms to disappear.

Because diarrhea of refractory type appears to be an early symptom in one third of the patients with noninsulin-secreting islet cell adenomas of the pancreas so far reported in the literature, more attention should be paid to it as a possible presenting symptom. In all 9 patients diarrhea was the earliest symptom and in only 5 did peptic ulceration occur later. In 1 the peptic ulceration appeared while the patient was being given adrenal cortical steroids in heavy doses to control the diarrhea.

Recognition of the fact that refractory diarrhea and hypokalemia may result from an underlying islet cell adenoma of the pancreas should lead to earlier diagnosis and surgical treatment of these patients.

CATECHOLAMINES

Changes in Plasma Concentration of Epinephrine and Norepinephrine with Muscular Work were studied by Irving Gray and William P Beetham Jr[3] (Natick Mass) with the technical assistance of Benjamin Mehlman Six young lightly clothed fasting men walked on a treadmill at 3 5 mph for 30 minutes They were transferred to a second treadmill where they ran for 5 minutes at 7 mph (2 could run for only 2 5 minutes) The run was an acute exhausting stress for all Epinephrine and norepinephrine were determined by the method of Weil Malherbe and Bone in blood samples taken after the walk and at intervals after the run

About a threefold rise in *norepinephrine* was noted 2 minutes after the run values returned to control levels in 15 30 minutes After the walk only 1 subject showed a change in either epinephrine or norepinephrine levels the latter increased *The epinephrine response to violent exercise* varied among the subjects and seemed to be correlated with the emotional response to the situation When elevated epinephrine returned to control levels as rapidly as did norepinephrine

Anti insulin Effect of Epinephrine Its Significance for Determination of Serum Insulin by Rat Diaphragm Method Glucose consumption by rat diaphragm is one method for calculating plasma insulin like activity but there are often large variations between test animals and sometimes a discrepancy between the serum insulin values and clinical findings It has been shown that undiluted serum has less insulin like activity than does serum diluted 5 10 times with buffer This has been considered to be due to an inhibiting substance the effect of which diminishes more rapidly on dilution than that of the serum insulin

J Groen H v d Geld R L Bolinger and A F Willebrands[4] (Amsterdam) found that addition of epinephrine to the medium in the absence of added insulin produced only a

(3) Proc Soc Exper Biol & Med 96 636 638 December 1957
(4) Diabetes 7 277 July Aug 1958

slight effect on glucose consumption but epinephrine strikingly suppressed glucose consumption when added to medium containing insulin in a concentration of 5×10^{4} units/ml. The degree of suppression of the insulin effect depended on the concentration of epinephrine and the effect was completely inhibited at concentrations of 10 µg/ml epinephrine or more. Inhibition was significant at concentrations as low as 10^{4} µg/ml epinephrine.

Norepinephrine in concentrations of 1 2 and 12 µg/ml slightly depressed basal glucose consumption in the absence of added insulin but it had a striking suppressive effect when insulin was present in a concentration of 5×10^{4} units/ml. Inhibition of insulin effect was complete at norepinephrine concentrations of 1 µg/ml and was significant at concentrations as low as 5×10 µg/ml. About 100 times as much norepinephrine was required to give the same depressing effect as epinephrine.

Addition of varying concentrations of epinephrine suppressed the insulin activity of diluted serum. No significant reversal of the inhibition by epinephrine of insulin was noted by use of blocking agents in the medium. There was no significant interference with the binding of labeled insulin by the diaphragm even though the rise in glucose consumption by insulin was blocked.

When serum is diluted the epinephrine activity is reduced more than the insulin activity. If a plasma epinephrine level of 10 µg/ml is present with a given insulin activity and the plasma is diluted 10 times the epinephrine level in the medium becomes 10^{3} µg/ml. This dilution could be expected to produce a change in the inhibitory effect on insulin from 90 to about 50. This could result in a serum insulin-like activity of 5 times that obtained in undiluted serum. This may be an important consideration in some cases of insulinoma in which even while the blood sugar is low normal or even low plasma insulin level sometimes have been found. Such patients with low blood sugars could be expected to have high epinephrine levels which would vitiate the results of plasma insulin determination by the rat diaphragm method. Variation in the amount of epinephrine in rat diaphragms may account for some variations between test animal

Probably inhibition by epinephrine is only indirect Epinephrine increases the concentration of active phosphorylase which increases the breakdown of glycogen forming lactic acid via glucose 1 phosphate and glucose-6-phosphate Glucose-6-phosphate inhibits the hexokinase reaction noncompetitively Therefore an increase in the concentration of glucose-6 phosphate caused by glycogenolysis would lead to decreased phosphorylation of glucose and diminished utilization of glucose from the medium

PHEOCHROMOCYTOMA

Pheochromocytoma Diabetes and Glycosuria P Freedman R Moulton M L Rosenheim A G Spencer and D A Willoughby (Univ College Hosp London) point out the association of glycosuria with pheochromocytoma in 3 patients in whom diagnosis was diabetes mellitus before the adrenal tumor was discovered and in a fourth who had glycosuria when first seen A systematic search including measurement of the excretion of pressor amines in the urine was made among 144 selected diabetics and 2 more possible cases were found

In each of the 4 with proved pheochromocytoma the initial history was obscure and many of the symptoms were considered manifestations of anxiety Symptoms included hypertension unexplained attacks of tenseness inability to move tachycardia with a feeling of impending death headache sweating glycosuria and a diabetic glucose tolerance curve Complete histories were obtained after diagnosis had been established by estimating the pressor amine content of the urine After removal of the tumor the pressor amine content of the urine returned to normal and symptoms subsided

Pheochromocytoma should be suspected in any diabetic with severe hypertension and in any hypertensive diabetic with unusual symptoms

Bilateral Pheochromocytoma Richard H Flandreau and Arthur S Glushien[6] (Univ of Pittsburgh) report a case in which bilateral adrenal pheochromocytoma was treated suc

(5) Quart J Med 7 30 3 1 J l 19 8
(6) A M A Arch Surg 6 626 J ry 1 58

cessfully by one stage total adrenalectomy This is believed to be the fourth instance of successful removal of bilateral pheochromocytomas in a single operation

Man 37 was believed to have chronic glomerulonephritis with secondary hypertension Clinical and x ray diagnosis of duodenal ulcer was made He also had excessive sweating unexplained fever postural tachycardia postural hypotension hyperglycemia and on one occasion glycosuria which aroused suspicion of a bilateral adrenal pheochromocytoma Absence of a precipitous drop in blood pressure after removal of the right adrenal pheochromocytoma indicated additional functioning chromaffin tumor tissue After both adrenals were removed shock developed which proved severe prolonged and almost refractory to treatment Postoperatively over 60 hours the patient was given an average of 115 μg levarterenol base and about 1 mg phenylephrine hydrochloride/minute or about 40 times the concentration ordinarily used of the former and 13 times that of the latter Administration of these drugs in such quantities and concentrations would have been impossible had not a polyethylene catheter been inserted into the inferior vena cava

Possibly the use of steroids preoperatively might have prevented or mitigated the shock but they had been withheld in view of the uncertainty as to the diagnosis of pheochromocytoma the lack of any suspicion that total bilateral adrenalectomy would be required and the reluctance to use steroids in a patient with bleeding peptic ulcer Hyponatremia may well have contributed to the perpetuation of shock and tachyphylaxis because pressor response to levarterenol and desoxycorticosterone depends on an adequate amount of sodium in the body and is weakened or abolished during salt withdrawal This patient responded better to vasopressor agents after the hyponatremia had been corrected

The persistence of hypertension after removal of a pheochromocytoma is a common but little understood phenomenon The blood pressure in this patient although not at a normal level has remained much lower than it was before operation and the regression of changes in the ocular fundi and the marked symptomatic improvement suggest that the prognosis has been greatly improved

Recurrent Pheochromocytoma Report of Case in Previously Treated Child is presented by Thomas E Cone Jr (US Naval Hosp Bethesda Md) The appearance of a second pheochromocytoma at a different site 2¼ years after

(7) J A M A 1 994 999 J 1 s

successful removal of the primary tumor has not been described previously in children

Boy 8 had a right suprarenal pheochromocytoma removed surgically in April 1955 Just before operation the concentrations of catechol amines in the plasma were 65 µg /L circulating norepinephrine and 4 8 µg /L epinephrine Ten days postoperatively the values were 8 1 µg /L norepinephrine and 0 7 µg /L epinephrine

For the next 2 years the patient was in excellent health Blood pressure was often checked during this period and values were consistently normal About 6 months before the current admission he had tonsillitis which was followed by persistent swelling of the right anterior cervical area This swelling continued to enlarge and was associated with Horner s syndrome on the same side

The concentration of catechol amines was above normal when he was readmitted in August 1957 (13 3 µg L circulating norepinephrine and 1 µg /L epinephrine) The blood pressure varied with systolic pressures of 155 185 and diastolic pressures of 120 150 mm Hg To prove that the mass in the right side of the neck was a functionally active pheochromocytoma a recently described method of selective venous catheterization with analysis of the blood for concentration of catechol amines at different sites within the venae cavae was used The values obtained at the varying sites in this patient indicated that the cervical mass was an active pheochromocytoma because the concentration of catechol amines in the superior vena cava was 2 3 times greater than that in the inferior vena cava The mass was removed and proved to be a functionally active pheochromocytoma Two days after operation the blood pressure was 140/100 5 days later it was 125/90 The concentrations of catechol amines in the plasma at this time were 3 8 µg /L norepinephrine and 3 2 µg /L epinephrine

Pheochromocytoma of Adrenal Gland with Granulosa Cell Tumor and Neurofibromatosis Report of Case with Fatal Outcome Following Abdominal Aortography Joaquin F Lopez[8] (Ohio State Univ) describes the eighth known case of association of pheochromocytoma and malignancy and the first of association with granulosa cell tumor

Woman 38 had multiple neurofibromatosis uterine leiomyoma and hypertension (235/130) Response to 15 4 mg benzodioxane was not indicative of pheochromocytoma although the Regitine® test was subsequently positive Abdominal aortography was done through a needle placed 1 cm. below the 12th rib into the aorta After nonvisualization a second injection was given and a tumor at the upper pole of the left kidney was clearly seen Shortly thereafter the patient went into shock This was followed by a steady rise in blood pressure acute heart failure and death

Autopsy findings revealed a large hematoma surrounding the left

(8) A n I t Med 48 187 199 J a y 1958

adrenal gland The gland contained a 5 cm pheochromocytoma which presented evidence of fresh hemorrhages and necrosis Metastatic nodules of malignant granulo a cell tumor were distributed in the peritoneum omentum and mesentery and replaced both ovaries and ovarian ligament Pressor substances in the adrenal tumor were 22 2 mg /Gm tumor tissue or a total of about 1 650 mg (normal 0 25 0 7 mg /Gm adrenal tissue) In the heart by use of the same method but concentrating with aluminum hydroxide the total catechol was 1 46 μg /Gm heart tissue (0 57 μg /Gm as epinephrine and 0 89 μg /Gm as norepinephrine) Normal total catechol values are about 0 25 μg /Gm tissue with an upper limit of 0 6 μg /Gm

This is apparently the third case of death following abdominal aortography in a patient with pheochromocytoma The mechanism of death appears to be adrenal crisis precipitated by intra adrenal and/or periadrenal hemorrhage with liberation of large amounts of pressor substances

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THE ADRENAL CORTEX

► One of the most fascinating developments of the past year is the discovery of the way the body controls the release of aldosterone Methods of assay have developed with remarkable rapidity close on its identification only 6 years ago and now the mechanisms controlling its release have been covered Two of the highlights of one of the best Laurentian Hormone Conferences ever held that of September 1958 were the presentations by Gordon Farrell and Frederic C Bartter of their original work on the control and physiologic action of aldosterone Both discovered independently that stretching the right atrium of the heart reduces the output of aldosterone whereas stretching the left does not This phenomenon is in harmony with the observation that aldosterone output is affected by failure of the right side of the heart but not of the left It also accords well with the now generally accepted concept that aldosterone secretion is a function of extracellular volume and specifically of the intravascular compartment in the right atrium and great vessel Since the compound causes retention of salt and water it makes sense from a homeostatic viewpoint that reduction of pressure on these vessels will cause retention of salt and water while an increased stretch will permit diuresis Farrell's studies have localized the controlling center in or near the pineal gland The neurohumor which control the secretion of aldosterone by the adrenal cortex apparently is elaborated by either the pineal gland or the subcommissural body It would be nice to assign a function to the pineal gland after all these years Since the pineal is a modified third eye in amphibians which spend part of their time in salt water and part on land it seems appropriate that this organ should be concerned with seeing that the salt content of body fluids is maintained at a normal level The increased excretion of aldosterone in toxemic pregnancy has now been shown to be typical of pregnancy and not specific for eclampsia Studies reported this year strongly suggest that the site of origin of aldosterone in pregnancy is either the placenta or the fetal adrenal since aldosterone excretion increases during pregnancy in women who

have been totally adrenalectomized A perplexing feature has been the lack of edema in primary aldosteronism an apparent contradiction which has been in part abrogated by the description of massive edema in more recently described cases Amphenone has been used to inhibit the production of adrenal cortical steroid and within the past year a chemical derivative has been described which appears specifically to inhibit 11 beta hydroxylation For the first time primary hypoaldosteronism has been reported as a clinical entity characterized by weakness giddiness fatigability hypotension and hyponatremia The dissociation of the various adrenal cortical stimulating activities of pituitary extracts has come in for renewed study Rimfret s earlier claim of obtaining adrenal weight maintaining activity from pituitary extracts devoid of ascorbic acid depleting activity has now been amply confirmed Whether this is the same substance found by Jailer in the blood of patients with Cushing s disease acromegaly and pregnancy and whether it is in truth responsible for the increased adrenal cortical activity of Cushing s disease remains to be established Tyler s observations that similar hyperreactivity follows repeated administration of subliminal doses of corticotrophin keeps the matter open It is now apparent that adrenal cortical function is subject to many other control including the thyroid gland ability of the liver to inactivate adrenal secretion anesthesia and surgical procedures Whether the widely accepted tests for differentiating Cushing s disease due to adrenal hyperplasia from the identical syndrome caused by adrenocortical tumor are truly reliable has also been reopened As in the past Cushing s syndrome has been observed in patient s with ovarian tumors but most recently it has also been seen in association with bronchogenic carcinoma perhaps because of metastases to the adrenal cortex Jailer s brilliant pinpointing of the exact enzymatic defect responsible for the various forms of congenital virilizing adrenal cortical hyperplasia has now been matched by its therapeutic counterpart namely achievement of pregnancy This success may partially explain the enthusiasm for the similar therapy of hirsutism in women on the assumption that it represents a milder form of adrenal overproduction of androgens Although chemical evidence of increased androgen production has been demonstrated in a few of these cases it is by no means established that adrenocortical therapy should be given to every girl with a few whiskers on her chin The diabetogenic action of corticoid is described in the section on Carbohydrate Metabolism The combination of Addison s disease and diabetes insipidus is reported in the section on the Neurohypophysis —Ed

Aldosterone Secretion

Special Article

CONTROL OF ALDOSTERONE SECRETION

by Frederic C. Bartter, M.D.

Three types of stimulus have been shown to influence aldosterone secretion corticotrophin potassium and some function of body fluid volume The evidence strongly favors the view that each may operate independently of the other

Corticotrophin has been shown to have a small but signifi

Chief, Section on Clinical Endocrinology, National Heart Institute

cant and reproducible influence on aldosterone secretion in the rat[1] dog and man[3] both in vivo and in vitro[4]

Potassium loading has been shown to increase aldosterone secretion and potassium depletion to decrease it. As the changes induced by potassium bear no relation to changes in hydrocortisone secretion they are almost certainly independent of changes in the concentration of corticotrophin. It also appears quite clear from studies designed to influence potassium balance independently of body fluid volumes that the effects of potassium need not depend on alterations in body fluid volume. When potassium depletion was produced in normal subjects who had been moderately sodium depleted urinary aldosterone fell significantly while intravascular volume (vide infra) did not change or *contracted* further. Conversely restoration of potassium gradually to potassium depleted subjects induced significant rise in urinary aldosterone while intravascular volume *expanded* significantly. Although the effects of potassium on aldosterone secretion may thus be shown independently of volume changes two studies[6] have confirmed the extreme sensitivity of the potassium depleted subject to expansion of extracellular fluid volume

There is strong evidence that humoral agents mediate the control of aldosterone secretion. Thus indirect evidence indicates that only small amounts are secreted by transplanted sheep adrenals unless perfused by blood from salt depleted animals. Isolated dog adrenals may be similarly stimulated with blood from donor animals whose venae cavae have been constricted[8] (vide infra). Dogs with mid collicular section secrete only small amounts unless infused with fresh extracts of brain. Extracts of diencephalon were found to exert moderate activity[9] and those of the region surrounding the pineal and subcommisural body marked activity[10]

Alteration in body fluid volume constitute the third type of stimulus affecting aldosterone secretion. It has been shown that aldosterone secretion may be increased by decreases in total body water and decreased by expansion of body fluid volumes with water alone. Relatively large changes in total body water induced relatively small changes in aldosterone secretion. When the volume of extracellular fluid rather than total body water was altered (as by changing sodium

intake) aldosterone secretion could be influenced by relatively much smaller changes in volume Finally the control of aldosterone could be mediated by even smaller change in intravascular volume alone phlebotomy with immediate restoration of the sodium withdrawn regularly increased urinary aldosterone red cell reinfusion regularly lowered it

As regards pathways by which volume stimuli may reach appropriate centers recent studies suggest a dual receptor system Constriction of the supradiaphragmatic inferior vena cava regularly increases aldosterone secretion and the release of such a constriction regularly lowers it As the increase can be prevented by the simultaneous infusion of blood above the constriction the effect may be attributed to a localized decrease of blood volume It was found that section of the vagus did not prevent the rise of aldosterone secretion with constriction but did prevent its fall after release *of constriction*[11] *This suggested that stimuli which lower* aldosterone secretion follow vagal pathways but those which raise it do not Dogs subjected to traction on the right atria have been reported to secrete less aldosterone than control animals[1] It is reasonable to suppose that the stimuli so produced and those described above requiring vagal pathways are the same

Increase of aldosterone secretion has been shown to result regularly from relatively slight constriction of the carotid arteries low in the neck That this increase can be prevented by denervation of the carotid arteries in the region surrounding the bifurcation suggests that stimuli which increase aldosterone secretion arise in the carotid itself Carotid constriction thus provides a mechanism whereby a localized limitation of blood volume may lead to increased aldosterone secretion even when (as for example in the patient with congestive failure) total blood volume may be greater than normal

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Effects of Diencephalic Mesencephalic Lesions on Aldosterone and Hydrocortisone Secretion were studied by Anna E Newman Edward S Redgate and Gordon Farrell[9] (Western Reserve Univ) Brain stem lesions (high frequency coagulation) were made in 35 large male cats 19 without lesions served as controls Four hours after lesioning the secretion rates of hydrocortisone and aldosterone were determined by isolating steroids from adrenal venous blood by paper chromatography Transection of the mid*brain reticular formation did not alter aldosterone or hydro*cortisone secretion rates Destruction of the ventral diencephalon significantly reduced hydrocortisone and aldosterone secretion Even greater reduction in aldosterone levels was effected by lesions in the reticular formation of the midbrain and caudal diencephalon These lesions likewise depressed hydrocortisone secretion Aldosterone secretion was significantly increased (4 cats) when the lesions extended caudally into the rostral half of the pons without affecting *hydrocortisone secretion (Fig 37)*

Recent neuroanatomic evidence for pathways from mesencephalic areas to the diencephalon are in excellent accord with the authors observations on the physiologic effects of mesencephalic lesions

In further studies the effects of a series of small lesions confined to the central gray substance and adjacent structures at the level of the posterior commissure were deter*mined In four of seven experiments significant reduction* in aldosterone secretion was *observed Precise correlation*

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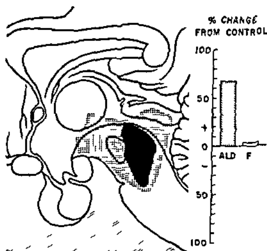


Fig 37 —C t al lr n t le s l l 1 ro tral po 4 t C h t hed cl f ll le ons n th g ou l l bl ck th t c nun t ll le ll pr h h w ld te on t n rea d t y 67% bo e contr l l l wh l y l oc t sore et on ma el t eo t l l l (3 5% abo nol on co t l l) (Court y of N wm n \ F t l E lc l gy 63 723 36 Decembe 19 8)

of the extent of reduction in aldosterone output with structures involved in the lesions has not yet been possible It seems evident that structures important in aldosterone regulation are present in this area

► [At the Laurentian Hormone Conference September 19 8 Farrell reported that the neurohumor which stimulates the releas of aldosterone from the adrenal cortex is present in greatest concentration in that section of the brain which contains the pineal gland the commissure and the subcommissural body —I d]

Influence of Position and Activity on Secretion of Aldosterone was investigated by Alex F Muller Elizabeth L Manning and Anne M Riondel[1] (Univ of Geneva) in 3 normal persons and in a hypophysial dwarf Urine was collected every 12 hours All were maintained on a constant low sodium diet and varied their activity and position by various patterns

The data demonstrate that position and activity influence urinary excretion of aldosterone whereas the taking of small amounts of salt at night instead of by day has no such influence An increased daily excretion of aldosterone can be considered as reflecting increased secretion of aldosterone by

(1) l et 1 711 713 Ap 5 1958

the adrenal gland A small change in diurnal and nocturnal intake of salt has no influence on the diurnal predominance of aldosterone excretion The greater excretion of aldosterone by day appears to result from erect position and activity concurrent with contraction of the effective blood volume as a result of standing and perhaps initiated by this decrease in volume The mechanism may also operate in hemorrhage and in congestive heart failure Retention and elimination of sodium coincide with increased and decreased secretion of aldosterone Thus it appears that increased retention of sodium with standing and exercise is caused by increased aldosterone secretion which in turn is caused by contraction of the effective blood volume Conversely bed rest increases the excretion of sodium by reducing secretion of aldosterone

However in the ambulatory person no correlation is found between day and night cycles of sodium and aldosterone This is consistent with the view that alterations in blood volume not only influence aldosterone secretion but also initiate acute renal adjustments in sodium excretion which appear to be independent of aldosterone This is corroborated by such mechanisms in patients with Addison's disease and by the constant diurnal nocturnal sodium excretion difference in the pituitary dwarf who was studied In the dwarf however there was no difference between diurnal and nocturnal secretion of aldosterone Prednisone therapy reestablished the diurnal predominance if the patient was active but not when recumbent The mechanism is unknown

Aldosterone Excretion Following Hypophysectomy in Man Relation to Urinary Na/K Ratio has been studied by J G Llaurado (Univ of Otago) Five patients with no apparent electrolyte imbalance before operation had hypophysectomy for generalized carcinomatosis Urinary aldosterone excretion was bioassayed in the adrenalectomized rat according to established procedure With this method the activity of the test material is indicated by a fall in the Na/K ratio The ratio is expressed as a percentage of the mean figure for a control group Thus a more intense effect is represented by a greater reduction of this percentage

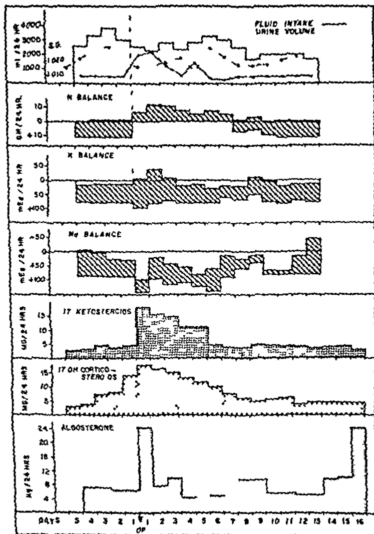
( ) M tab I m 6 556 563 N ml 195

The well established drastic reduction in the Na/K ratio which occurs after nonendocrinologic operations was not present in these hypophysectomized patients who demonstrated only a moderate reduction in the Na/K ratio The patients failed to show the great increase in aldosterone excretion which is found after any nonendocrinologic operation and showed only a slight increase These findings demonstrate that hypophysectomized patients do not have the normal metabolic response to operation Present evidence favors diencephalic control of aldosterone secretion Presumably a diencephalic center is deranged or damaged by hypophysectomy and hence the usual large increase in aldosterone does not occur The persistent production of aldosterone by the adrenal cortex after hypophysectomy shows that a certain basal amount of aldosterone is being released by the adrenal cortex independently of the circulating trophic hormone elaborated by the diencephalon To assess whether this diencephalic center has been damaged temporarily or permanently it would be of interest to study the effect on aldosterone excretion of a subsequent nonendocrinologic operation or of accidental trauma to a hypophysectomized patient The study seems to provide indirect evidence that aldosterone production is stimulated by a diencephalic center which is functionally or anatomically damaged during hypophysectomy

Aldosterone Excretion Following Trauma was studied by Eleanor H Venning J R McCorriston I Dyrenfurth and J C Beck[3] (McGill Univ) The physiologic and metabolic response to gastrectomy showed essentially a similar pattern in the 3 patients studied although the intensity of this response varied depending somewhat on the extent of the operative damage These patients were in a good nutritional state preoperatively and on the day of operation all showed an immediate rise in the excretion of 17 hydroxycorticosteroids and aldosterone The former remained at a high level for several days then gradually returned to the preoperative level

Patient F K (Fig 38) who had the most extensive operation showed the greatest respon e and the subsequent met

(3) Metab 1s 7 (pt 1) 93 300 J ly 1958



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abolic and endocrine changes were those associated with the development of surgical complications

In all these patients aldosterone excretion rose to significantly higher levels on the day of operation In 2 this increase lasted for 1 day only and on the 2d postoperative day the values were within normal range All 3 showed a later rise in aldosterone excretion in patient F K this appeared to be associated with recurrence of vomiting and development of dehydration (day 16 Fig 38) and in another patient with wound infection

Despite the increased output of aldosterone on the day of operation only patient F K showed significant sodium retention on this day This patient received a much greater intake of sodium on this day than did the other 2 which might account for the excessive retention of sodium After the day of operation all 3 patients showed progressive retention of sodium for several days though aldosterone excretion had decreased to lower levels It would appear therefore that unless there is a delay in the effect of aldosterone on sodium metabolism the sodium retention that normally occurs postoperatively cannot be attributed to the increased secretion of aldosterone Other adrenal steroids which are elaborated in greater amounts at this time must contribute to this metabolic change

There was an immediate loss of nitrogen and potassium after operation the former being more prolonged than the latter The potassium nitrogen ratio of the negative balance was greater than 3 5 on the day of operation in 2 patients which suggested that more potassium was being lost than could be accounted for by protein catabolism Since aldosterone causes potassium excretion in the adrenalectomized animal this excessive loss of potassium might be associated with the increased aldosterone secretion

A marked reduction in urine volume with a corresponding rise in specific gravity which lasted 24 48 hours postoperatively was also observed in the 3 patients The sodium retention that occurred later was not associated with increased urinary concentration

In this present study the initial increase in aldosterone excretion observed after operation occurred at a time of adre

nal stimulation As other factors which tend to suppress aldosterone excretion come into play such as sodium and water retention a reduction in secretion of the hormone follows

In studies carried out on 2 patients after fractures no urine was obtained on the day of injury Aldosterone excretion appeared to be depressed however for several days after the accident

Aldosterone Excretion in Patients with Cirrhosis of the Liver has been studied by Inge Dyrenfurth C H Stacey J C Beck and Eleanor H Venning[4] (McGill Univ) in 30 determinations on 11 patients Values obtained from 23 nor

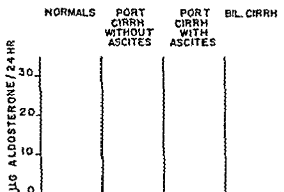


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mal subjects ranged from 1 to 7 3 µg /24 hours with a mean of 3 86 ± 0 38 µg Repeated determinations on 4 patients diagnosed as having biliary or portal cirrhosis without ascites were within normal range (Fig 39) Only in the 7 patients who had portal cirrhosis with ascites was a marked elevation of aldosterone excretion found

The effect of paracentesis was studied No correlation was found between the level of urinary aldosterone before paracentesis and the amount of fluid that could be withdrawn After paracentesis three phases of aldosterone excretion were observed Initially there was increased decreased or even unchanged aldosterone excretion lasting for 1 2 days

(4) M [illegible] 6 544 555 N mbe [illegible]

This was always followed by a rise in aldosterone level which was correlated with reaccumulation of abdominal fluid. This second phase lasted up to 6 days and was followed in most cases by a third phase in which aldosterone decreased again before the next paracentesis was required. In general it appeared that the rate of active accumulation of ascitic fluid was a better index of aldosterone influence than the amount of fluid accumulated. It also appeared that the mechanism suggested for aldosterone secretion in normal persons does not hold for patients with cirrhosis of the liver.

The aldosterone content of abdominal fluid was determined in a few instances. The free aldosterone fraction ranged from 0.058 to 0.113 μg./100 ml. and the total from 0.108 to 0.233 μg./ml.

Infusion of Aldosterone, 9α-Fluorohydrocortisone and Antidiuretic Hormone into Renal Artery of Normal and Adrenalectomized Unanesthetized Dogs. Effect on Electrolyte and Water Excretion was studied by A. C. Barger, R. D. Berlin and J. F. Tulenko[5] (Harvard Med. School). A technic was used for chronic catheterization of one renal artery with collection of urine from each kidney individually.

In the normal dog, intra-arterial aldosterone or 9α-fluorohydrocortisone produced unilateral kaluresis but no demonstrable natriuresis or effect on water excretion. In the same catheterized dogs after recovery from adrenalectomy, small doses of aldosterone infused into the renal artery produced unilateral antinatriuresis. The unilateral kaluresis was of the same magnitude as that observed in the normal state. In the normal and adrenalectomized animals the effect of intrarenal aldosterone on potassium excretion was apparent only after a delay of 30-60 minutes and maximum effect was noted after 2-3 hours.

The present investigation also clearly indicates the local renal action of antidiuretic hormone on water excretion and the rapidity of its action. No natriuresis was observed with antidiuretic hormone in normal dogs on water diuresis.

► [August, Nelson and Thorn (J. Clin. Invest. 37: 154, 1958) have also reported that prolonged administration of aldosterone caused an initial gain of weight and sodium retention, both of which disappeared during continued administration of the hormone. Potassium secretion, on the other

(5) Endocrinology 62: 804-815, June 1958.

hand increased throughout the period of treatment It may be that the usual lack of edema in primary hyperaldosteronism results from inability of the potassium-depleted renal tubule to retain fluid —Ed]

Inhibition of Sodium Retaining Influence of Aldosterone by Progesterone was studied by Richard L Landau and Kathleen Lugibihl[6] (Univ of Chicago) Progesterone (50

Fig 40—Eff t f p g t v x t f d hl i p t m i t I i t d d g f ld t p t m u ts f b l g lly t d ld t B ke h ontal I d t ag f t l l tlq h t h g d t g h t h ft (C t f L da R L a d L g b hl K J Cl n E I 1 18 1 37 1 45 N mb 1958)

mg/day) elicited a pronounced natriuretic response in a woman aged 46 with Addison's disease who was treated with aldosterone and 50 mg cortisone acetate/day intra muscularly (Fig 40) After aldosterone was discontinued

(6) J Cl E dx 1 18 1 37 1 45 N mb 1958

the same amount of progesterone had no influence on urinary sodium excretion

In studies performed in two other adrenal deficient patients 150 mg progesterone nullified the sodium retaining effect of a slow intravenous infusion of 20 µg aldosterone Under the same circumstance progesterone alone had no influence on urinary sodium excretion The same quantity of progesterone failed to block the effect of 40 50 µg aldosterone

The results were interpreted a demonstrating that progesterone is an antagonist of aldosterone presumably at the level of the renal tubules It was accordingly assumed that the natriuretic influence of progesterone in normal persons is due to inhibition of endogenous aldosterone In any consideration of control of sodium metabolism during pregnancy and the luteal phase of the menstrual cycle this competitive interaction of progesterone and aldosterone must be given a major role

Influence of Intravenously Administered Adrenal Steroids on Sodium and Water Excretion in Normal and Addisonian Subjects Joseph F Dingman John T Finkenstaedt John C Laidlaw Albert E Renold Dalton Jenkins John P Merrill and George W Thorn (Harvard Med School) report that the effect of adrenal steroids on renal excretion of sodium and water during these short term studies (8 24 hours) was predominantly due to alterations in renal tubular function rather than to variations in glomerular filtration rate Hydrocortisone especially in small doses and prednisone often produced a decline in tubular reabsorption of sodium and a short lived natriuresis within the first few hours of administration This transient natriuretic effect of hydrocortisone was blocked by large doses of desoxycorticosterone acetate (DCA) but was not influenced by smaller doses

Retention of sodium related to increased tubular reabsorption was produced by aldosterone corticosterone and DCA Sodium retention was also produced by large doses of hydrocortisone and observed after the transient natriuresis evoked by small doses The diuresis of free water observed on ad

ministration of hydrocortisone, prednisone or aldosterone was attributable to decreased distal tubular reabsorption of water possibly related to inhibitory effects of these steroids on secretion of antidiuretic hormone from the neurohypophysis.

Excretion of Sodium Retaining Factor by Cortisone Treated Adrenalectomized Hypertensive Patients was compared with that found among nonadrenalectomized hypertensive subjects by K. J. Carerd and D. M. Green[8] (Univ. of Southern California). The 24-hour urinary output of sodium retaining factor was determined by a bioassay technic using Na.

The sodium retaining factor by the adrenalectomized patients all fell within the upper half of the range for nonadrenalectomized subjects. The average value for the group equivalent to 3.77 μg. desoxycorticosterone acetate (DCA) was 76% above the mean of 2.14 μg. found in the patients not operated on. However, this difference was not statistically significant ($0.1 < P < 0.2$).

The 24-hour urinary sodium excretion was 79% higher among adrenalectomized patients, averaging 163 mEq./sq. m., compared with 91 in subjects not operated on ($0.001 < P < 0.01$). This difference was due primarily to an increased urinary sodium concentration (155 mEq./l. compared with 93). The urinary water outputs were not materially different. Individual sodium retaining factor outputs were variable and were not correlated with any other measured function.

The higher sodium output observed in the cortisone treated adrenalectomized subject mimics the increased sodium exchange seen in DCA treated rats permitted self selected salt intakes and is consistent with the concept that the glucocorticoids may at times promote sodium excretion.

Studies on Origin of Aldosterone during Human Pregnancy were made by John C. Laidlaw, Max Cohen and Allan G. Gornall[9] (Univ. of Toronto). A progressive increase in urinary excretion of aldosterone occurs normally during human pregnancy. Level reached during the 3d trimester (alt

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(9) [illegible] 1 18 [illegible] 19

intake 7 8 Gm) have ranged from 21 to 125 µg/day with a mean of 47 µg in nonpregnant women the levels are le than 10 µg/day The increased urinary aldosterone during pregnancy may represent increased secretion of the hormone from the maternal adrenal cortex or po sibly production from some extra adrenal source such as the placenta or fetal adrenal These alternatives could be investigated in 2 preg nant women who had previously undergone complete bilat eral adrenalectomy for Cushing s syndrome One delivered a normal infant the other noted fetal movements up to the 36th week was subsequently delivered of a stillborn infant

The amount of aldosterone excreted by these patients was no more than one tenth the average excreted by normal pregnant women in the 3d trimester The finding of a uri nary excretion of 4 4 µg/day aldosterone during the 3d tri mester and less than 0 5 µg/day during the postpartum period in 1 patient suggested that the placenta or fetal adre nal cortex or both might be a source of small amounts of aldosterone during pregnancy Traces of aldo terone might have arisen from metabolism of administered hydrocorti sone in these tissues or elsewhere in the body

The major source of urinary aldosterone during pregnancy must therefore be sought outside the placenta or fetal adre nal The increase is probably due mainly to increased secre tion from the maternal adrenal cortex Since present meth ods measure only aldosterone and none of its po sible metabolites part of the increase may be due to a depres ed metabolic transformation during pregnancy as has been demonstrated for hydrocortisone In any case it seems rea sonable that the high output of aldosterone during preg nancy i not requisite for healthy gestation and serves no apparent purpose

Effects of Pregnancy on Adrenal Steroid Metabolism were studied by J D Martin and Ivor H Mills[1] (St Thomas Med School London) in 76 patients who had a normal pregnancy and in 24 with toxemia Plasma hydro cortisone was determined by paper chromatography and urinary 17 ketosteroids and 17 ketogenic steroids by the method of Gib on and Norymberski

The mean normal plasma hydrocortisone in 26 women was 17 7 µg/100 ml In pregnancy the plasma hydrocortisone was between 16 and 25 µg/100 ml The mean value tended to rise during pregnancy from 79 to 124 µg/100 ml except for a fall at 21 24 weeks to 54 There was no difference between the values in normal and toxemic pregnancies The 17 ketosteroids as determined by the Zimmermann reaction were mostly in the normal range (5 17 mg/day) A slight fall occurred at 21 24 weeks A rise occurred in late pregnancy which probably was due to the 20 ketone metabolites of progesterone The normal and toxemic patients had values in the same range The 17 ketogenic steroids were mostly in the normal range (5 18 mg/day) but tended to rise as the pregnancy progressed The results in normal and in toxemic pregnancies had similar distributions

The raised plasma hydrocortisone levels with normal amounts of urinary metabolites are interpreted as being due to reduced breakdown by the liver This alteration in the metabolism of hydrocortisone during pregnancy may be due to the effect of estrogens

Primary Hyper and Hypoaldosteronism

Primary Aldosteronism Clinical Staff Conference at National Institutes of Health Frederic C Bartter and Edward G Biglieri present 2 cases and review the rationale for use of a low sodium diet as a diagnostic and therapeutic tool in primary aldosteronism

Case 1—Boy 13 showed increased urinary aldosterone values after loading with potassium which is what might have been anticipated if the early low values had been due to potassium depletion On sodium deprivation urinary sodium level fell almost to zero but urinary aldosterone did not increase The hypokalemic alkalosis did not recur as long as sodium was withheld from the diet but returned when dietary sodium was increased (unless supplementary potassium was also given) Most of the urinary aldosterone values on a high sodium intake were above normal Because it was clear that the patient did not have a large tumor Δ 1 9α fluorohydrocortisone was given for several weeks to produce atrophy of normal adrenal tissue At operation two very small adrenals were found and were subtotally removed They were histologically normal Follow up showed that the patient

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remained completely normal clinically and chemically when receiving 20 mEq sodium daily but became hypertensive when sodium intake was increased and acutely hypotensive when it was reduced A standard dose of corticotrophin intravenously produced clearly subnormal responses in urinary and plasma 17 hydroxycorticoid

CASE 2—Man 27 had persistent hypertension for at least a year (200/160 mm Hg) The ECG showed left ventricular hypertrophy and strain An intravenous urogram showed downward displacement of the right kidney by a calcified adrenal mass (Fig 41) Serum electrolytes on two occasions were sodium 147 and 149 mEq/L potas



F g 41—I t g h w g d wnw 1 d pl t of ght k l 3 c l m dep t t t f ght d l d n m (Cou t y f B rtt F C d B gl F C \ I t M d 48 647 654 M ch 1958)

sium 2 6 and 2 4 mEq/L CO_2 content 33 and 36 mEq/L and chloride 101 and 102 mEq/L During an 8 hour intravenous infusion of corticotrophin serum 17 hydroxycorticoids and urinary 17 hydroxycorticoids increased less than normal but the eosinophil decreased from 218 to 26/cu mm When water was withheld for 24 hours urine osmolarity rose to only 535 mm/kg water indicating pronounced impairment of concentrating ability Inulin clearance was 108 cc/minute Two urinary aldosterone values on a normal diet with 250 mEq added sodium were 39 and 41 μg/24 hours (normal below 10 μg)

On readmission a month later he showed reduction in the hypertension and reversion of chemical abnormalities generally toward normal although there had been no intervening therapy On a high sodium intake the urinary aldosterone excretion remained high After

sodium deprivation urinary aldo terone excretion did not increa e but urinary sodium fell into t to zero over 2 weeks and the hypokale mic alkalo is di appeared Hydrocorti one produced no natriure i but did sharply increa e endogenou creatinine clearance These find ings support the diagnosis of aldo teroni m At operation a 6 cm adrenocortical adenoma was removed Po toperatively the urine pH fell from alkaline levels to about 5 89 6 84 and the blood pres ure gradually fell The patient became clinically and chemically well

Salt losing nephritis constitutes the greate t problem in differential diagnosi This differentiation is facilitated by u e of a low sodium diet Patients with primary aldosteron ism and little or no renal damage on a low sodium diet will show urinary sodium reduced virtually to zero thus ruling out a primary tubular odium lo ing lesion

Conn s Syndrome was studied by P K M Barrett K I S Bayliss and J R Rees [3] Diagno tic criteria may be fallible especially if incomplete and diagnosis may be establi hed on adrenal exploration

Woman 47 had had several neurologic incidents with confu ion On high pota sium intake (224 mEq daily) positive potassium bal ance of about 820 mEq wa achieved over 14 days initial negative sodium balance of about 180 mEq by the 5th day was rever ed by the end of the period On low pota sium intake (47 mEq daily) negative potassium balance of 88 mEq and positive sodium balance of 350 mEq occurred over 5 days A further balance tudy was started on the 12th postoperative day Over the next 5 days 70 mEq pot issium was retained and 185 mEq odium lo t On a diet containing 22 mEq sodium daily marked odium retention occurred with average sodium excretion 12 mEq daily over 7 days No tumor could be demonstrated on the pneumogram and history of previou urinary infection with a positive urinary culture favored a diagnosi of pota sium losing nephritis A typical adrenal adenoma was found on operation and the patient re ponded in the u ual way to it removal

Becau e of the unu ual features in this case distinction be tween potassium lo ing nephritis and Conn s syndrome could not be made before operation Absence of pyelonephri tis in the renal biopsy balance data and response to low so dium intake favored Conn s syndrome but ab ence of alka losis and hypernatremia normal odium potas ium ratios and failure to demonstrate increased urinary aldo terone ex cretion were unusual

Observations on Case of Primary Aldosteronism are pre sented by Milton G Crane Gordon Short and John E Pe

(3) P oc R y Soc Med 51 0 7 S pt mbe 1958

terson[4] (College of Med Evangelists Los Angeles Calif) This woman 43 differed from other patients described in the literature in that she had no chemical evidence of extracellular alkalosis and the excretion of mineralocorticoids in the urine was normal or only slightly elevated The biologic decay time of radioactive sodium was 40 days before surgery and 10 days after removal of a benign adrenal cortical adenoma both tests being performed with high sodium ingestion High intake of extra sodium chloride produced edema and headaches Headache is a presenting symptom in such patients along with hypertension spells of muscle weakness polydipsia and polyuria Symptoms hypertension and electrolyte disturbances were relieved by removal of the adenoma

Experience with this and previously reported case suggests that a patient with primary aldosteronism should be given adrenocorticotrophin and supplemental potassium chloride for about 3 5 days preoperatively to remove some of the extra sodium and to correct part of the potassium deficit

Case of Massive Edema in Association with Aldosterone Secreting Adrenocortical Adenoma which was strikingly contrasted with the accepted features of Conn s syndrome by the presence of extreme sodium retention high urinary excretion of aldosterone normal serum electrolytes and normal blood pressure is detailed by Eric J Ross Jean Crabbe Albert E Renold Kendall Emerson Jr and George W Thorn (Harvard Med School)

Woman 27 had edema pleural effusions and ascites on hospitalization Extreme sodium retention was demonstrated over the next 10 years with outputs of 2 4 mEq/day while on an intake of 48 mEq/day There was marked resistance to the many diuretic agents tried and a satisfactory sodium diuresis was obtained only when amphenone B an agent which suppresses adrenocortical activity was used This substantiated the suspected role of the adrenals in the sodium retention and at laparotomy an aldosterone secreting adrenocortical adenoma was removed The adenoma was thought to be related to secondary hyperaldosteronism which resulted from the prolonged and massive edema Removal of the adenoma resulted in temporary disappearance of aldosterone from the urine sodium diuresis and weight loss Recurrence of hyperaldosterone symptoms followed however and the second adrenal gland was removed This was fol

(4) Am J M 1 4 313 3 Februy 19 8
( ) Ibid 2 8 9 Aug t 1958

lowed by absence of aldosterone from the urine sodium diuresis and weight loss Nevertheless the patient still is very edematous (estimated 10 15 L of edema fluid) apparently because of abnormal capillary permeability Reduction of weight below a certain level and loss of edema fluid are regularly followed by symptoms of sodium depletion

The adenoma appears to have been the only adrenal tissue secreting aldosterone despite the presence of a stimulus which presumably acted equally on both glands When the adenoma was removed and a loss of body water was prompted by vigorous therapy directed at weight reduction the other gland began to secrete aldosterone The analogy between this situation and that in which a 17 hydroxycorticoid secreting adenoma is present with concomitant atrophy of the remainder of the adrenal cortical tissue is apparent In the present case however the stimulus is not pituitary adrenocorticotrophin since 17 hydroxy and 17 ketosteroids were secreted in normal amounts

The case also affords an illustration of the usefulness of amphenone in the diagnosis of clinical syndromes due to excessive production of adrenal steroids

Hypoaldosteronism with Otherwise Intact Adrenocortical Function Resulting in Characteristic Clinical Entity is reported by Bengt Skanse and Bernt Hokfelt[6] in a woman 56 The case was not associated with any coexistent disease and thereby appears to be the first case of pure hypoaldosteronism on record The clinical picture was characterized by dizziness faints weakness easy fatigability hypotension and hyponatremia without any measurable aldosterone in the urine Excretion of 17 ketosteroids 17 ketogenic steroids and of blue tetrazolium reacting corticoids was normal as was the response to administration of corticotrophin Serum electrolyte levels were entirely normal urine concentrated to 1 023 after 12 hours of fluid deprivation Its pH was 6 0 and endogenous creatinine clearance was 136 ml /minute The history clinical picture and laboratory findings argued against other adrenal cortical defects There was no evidence of a primary renal disorder Sodium restriction resulted in decreased urinary sodium which owing to the absence of any measurable amount of

(6) A t doc 1 8 9 36 M y 19 8

aldosterone in the urine was probably due to increased production of hydrocortisone.

Studies on this patient do not allow any conclusion as to whether the *primary error of metabolism was located* within the adrenal gland or affected some extra-adrenal regulatory mechanism.

Regulation of Adrenocortical Function

Hormonal Regulation of Pituitary Adrenocorticotrophin. Changes in pituitary corticotrophin content and concentration in rats after administration of various hormones for 1 week and after adrenalectomy were studied by Julian I. Kitay, Donald A. Holub and Joseph W. Jailer (Columbia Univ.). A modification of the Saffran and Schally technic of in vitro bioassay of corticotrophin was used. The validity and reliability of the technic were determined by comparison *of the potencies of several corticotrophin preparations* with those obtained by the ascorbic acid depletion method and by reassay of the same unknown. The results indicated satisfactory validity and reliability and showed a maximum error of 15%.

Adrenalectomy was followed by a significant rise in pituitary corticotrophin content associated with pituitary hypertrophy. This result confirms previous reports and is consistent with the hypothesis that a decrease in the circulat*ing level of adrenal steroids is followed by accelerated pro*duction of corticotrophin. Conversely, an increased steroid level produced by cortisone administration was followed by depletion of pituitary corticotrophin. The associated adrenal atrophy suggests that corticotrophin secretion was also decreased. These findings suggest that administration of cortisone for 7 days reduced corticotrophin synthesis with concomitant diminution of corticotrophin secretion.

Administration of epinephrine for 7 days was associated with *significant depletion of pituitary* corticotrophin similar to that obtained with cortisone. However, adrenal hypertrophy, presumably due to increased corticotrophin secretion, also was observed, in contrast to the cortisone-induced adrenal atrophy.

(7) Proc. Soc. Exper. Biol. & Med. 97:165-169, Jan., 1958.

The significant rise in pituitary corticotrophin content after corticotrophin administration was surprising The expected finding would have been pituitary corticotrophin depletion similar to that found in cortisone treated animals since the only commonly accepted effect of corticotrophin is stimulation of the adrenal cortex The observed increase was of such magnitude that it could not be explained by the possibility of contamination of the extracted pituitary glands with blood containing even large amounts of corticotrophin Experiments in progress involving administration of corticotrophin to adrenalectomized rats indicate that this increase in pituitary corticotrophin is not mediated by the adrenal gland At least three alternative explanations are suggested (1) increased blood corticotrophin may inhibit pituitary corticotrophin release (2) an increased circulating level of corticotrophin may stimulate corticotrophin synthesis or (3) the pituitary may adsorb corticotrophin when present in the blood in increased concentration

► [These authors have subsequently reported (J Clin Invest 38 291 1959) that in the rat administration of corticotrophin neither prevents nor ameliorates the reduced pituitary content of corticotrophin resulting from treatment with cortisone Clinically the adrenal can be restored to function by administration of corticotrophin after the inhibition produced by administration of cortisone or in Cushing's syndrome Kyle has described failure of the pituitary to resume elaboration of corticotrophin after a functioning adrenal tumor has been resected a condition we previously dubbed hypocortic trophic Addison's disease from Crooke's changes (Gordan and Lisser *Endocrinology in Clinical Practice* [Chicago Year Book Publishers Inc 1953] p 158) —Ed]

Relationship between Endogenous Antidiuretic Hormone Activity and ACTH Release in Man Antidiuretic hormone vasopressin has been postulated to be the neurohormone responsible for stimulating corticotrophin release If this is true plasma hydrocortisone levels should increase when endogenous antidiuretic hormone is released To test this Roger K McDonald Henry N Wagner Jr and Virginia K Weise[8] (Nat'l Inst of Health) determined the urine osmolality and plasma hydrocortisone levels in 15 normal subjects who were dehydrated and overloaded with water given hypertonic saline and nicotine made hypoglycemic by insulin and whose hands were immersed in ice water If the plasma hydrocortisone concentration increases 3 μg /100

(8) Proc Soc Exper Biol & Med [illegible]

ml 30 or more minutes after such test stimuli corticotrophin release can be presumed

When the patients were deprived of water persistent antidiuretic hormone activity could be demonstrated but plasma hydrocortisone levels decreased in the same way as when antidiuretic hormone was suppressed With hypertonic saline infusions endogenous antidiuretic hormone was present but plasma hydrocortisone levels did not rise When nicotine was injected intravenously into 4 subjects 2 showed no rise in plasma hydrocortisone despite a rise in urine osmolality When the hand was immersed in ice water for 2-6 minutes 5 of 8 subjects showed an increase in urine osmolality consistent with antidiuretic hormone release but 2 of these showed no increase in plasma hydrocortisone concentration One of the 3 who had no increase in urine osmolality manifested a rise of 8 µg/100 ml plasma hydrocortisone Thus 3 of the 8 had no evidence for simultaneous release of antidiuretic hormone and corticotrophin With insulin induced hypoglycemia there was also no correlation between change in urine osmolality and change in plasma hydrocortisone concentration

The data indicate that in normal human subjects endogenous antidiuretic hormone may be released without an increase in corticotrophin release and increase in corticotrophin release may occur without evidence of antidiuretic hormone release The observations fail to support the concept that endogenous antidiuretic hormone release stimulates release of corticotrophin

Pituitary Adrenal Axis Acute Adrenocortical Insufficiency and Persistent Occult Dysfunction Following Thermal Injury are reported by Paul Mandelstam Joseph W Goldzieher Harry S Soroff and Norris Green[9] in a man 21 He had been in excellent health before he was severely and extensively burned He responded well to hormone therapy which was not required after skin coverage was completed Although the concentration of plasma hydrocortisone and the urinary excretion of 17 hydroxycorticoids were normal there was failure to respond to exogenous corticotrophin with other evidences of adrenocortical abnormalities

(9) J Clin Endoc 18 84 99 March 1958

This refractoriness to exogenous corticotrophin could not be attributed to the presence of adrenocortical remnants functioning maximally under the stimulus of high levels of circulating corticotrophin since the plasma level of corticotrophin was not elevated. A more likely explanation was the possibility that adrenocortical secretions became independent of corticotrophin regulation.

Activation of Hormonal Secretions is described by P. K. Dasgupta and F. G. Young[1] (Univ. of Cambridge) who found in certain anterior pituitary preparations an adrenal growth maintaining material that is devoid of adrenal ascorbic acid depleting capacity in the hypophysectomized rat. Other investigators have also found that various pituitary preparations have similarly divergent action on the adrenal cortex.

The authors found that their crude sterile alkaline extract of ox anterior pituitary, which is devoid of ascorbic acid depleting activity, acquires this activity after extraction with acid acetone or if its pH is lowered to 3.0. Activity is obtained if the pH of the injected material is left at pH 3.0 or brought back to pH 8.0 immediately before injection and whether or not any precipitate formed in adjusting the pH to 3.0 is spun off before the biologic test is carried out.

Furthermore, adrenal ascorbic acid depleting activity appears when the crude extract is treated with urea (3.5M). It is convenient to refer to the starting material as precorticotrophin.

Because precorticotrophin acquires adrenal ascorbic acid depleting activity after such mild treatment as adjustment of pH to 3.0 or addition of urea (which might be expected to break hydrogen bonds), the change is unlikely to involve the fission of a covalent bond, i.e., it is more likely to be a physical or physicochemical than a chemical change. The nature of the change and its possible catalysis under biologically significant conditions, such as under the influence of enzymes, are under investigation. The question of the possible effect of precorticotrophin on the secretion of adrenal steroids also merits attention.

► [The discrepancy between adrenal weight maintenance and adrenal ascorbic acid depleting capacity of pituitary extracts was noted a early

(1) Nature 18 3 33 July 5 1958

as 1951 by Young's group (Nature London 168 1084 1951) and independently by Reinhardt and Li (Proc Soc Exper Biol & Med 77 229 1951) Jailer found a substance in the blood of patients with Cushing's disease which had adrenal weight maintaining capacity but did not discharge ascorbic acid Similar material was found in the blood of patients with active acromegaly and of women in late pregnancy Whether the substances are identical and in fact where the adrenal weight maintaining substance is elaborated is not established —Ed]

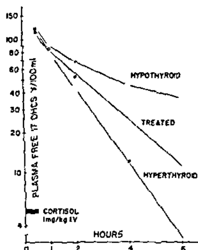
Behavior of C^{14} Cortisol and Estimation of Cortisol Production Rate in Man C L Cope and E G Black (Post grad Med School London) studied the behavior of C^{14} cortisol and C^{14} cortisone acetate after oral administration in 8 human subjects with each steroid A mean of 86% of the former and 76% of the latter appeared in the urine in the form of metabolites in the first 24 hours Only 1 5% of the dose appeared in chloroform soluble form and about one third of this was unchanged C^{14} cortisol or C^{14} cortisone From 16 to 20% usually appeared in a form rendered chloroform soluble by hydrolysis with beta glucuronidase and this fraction is composed largely of tetrahydrocortisol and tetrahydrocortisone

Tetrahydrocortisol and tetrahydrocortisone have been shown to have the same specific activity The specific activity of the excreted cortisol frequently differs from that of the tetrahydro compounds

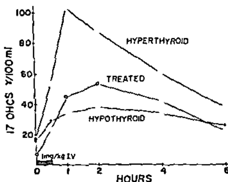
A method is proposed whereby an estimate of daily cortisol production can be obtained from a knowledge of the C^{14} content of the 24 hour urine plus the specific activity of the tetrahydro compounds in that urine Daily cortisol production of resting convalescent subjects has varied from 4 2 to 24 mg /day with a mean of 11 3 mg when determined by this method

Metabolism of Free and Conjugated 17 Hydroxycorticosteroids in Subjects with Thyroid Disease is affected by the type of dysfunction according to Harold Brown Edwin Englert Jr and Stanley Wallach[3] (Univ of Utah) Intravenous infusion of 1 mg /kg cortisol (hydrocortisone or Kendall's compound F) was given to 8 patients with hyperthyroidism 6 with hypothyroidism 6 with hyperthyroidism who had been treated and to 14 normal subjects Hyperthyroidism even when treated led to more rapid disappearance

(?) Cl S 17 147 1(3 Fb y 19 8



F g 4 —M a l f f l hyd cort t ds pl m ft f n f rt l (Cou t y f B w H J Cl E doc l 18 167 1 0 F b y 19 8)



F g 43 —M l f f onj gat d 17 hyd ort t d n pla m ft f on f rt l (C te f B w H J Ch E doc L 18 167 179 Feb y 1958)

of the free plasma 17 hydroxycorticosteroids than that observed with hypothyroidism after administration of cortisol and to higher levels of conjugated 17 hydroxycorticosteroids (Figs 42 and 43)

Similar infusions of tetrahydrocortisone in 3 patients with myxedema and 2 with thyrotoxicosis indicated that conjuga

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(2) Cl S 17 147 163 February 1958
(3) J Cl E doc | 18 167 179 Feb ry 1958

roids from the plasma as well as of the response to corticotrophin and of the urinary excretion of these steroids Such analysis suggests that adrenocortical activity varies directly with the BMR

► [A number of similar reports in the past year have confirmed these data Howard and Migeon (this YEAR BOOK p 254) found a similar delay in the metabolism of hydrocortisone in a patient with hypothyroidism secondary to hypopituitarism In their patient Cushing s disease medicamentosa developed from administration of small doses of corticoids —Ed]

Metabolism of Free and Conjugated 17 Hydroxycorticosteroids in Subjects with Liver Disease was appraised by Edwin Englert Jr Harold Brown Stanley Wallach and E L Simons[4] (Univ of Utah) in a study of patients with cirrhosis Levels of free and conjugated 17 hydroxycorticosteroids in plasma were measured after administration of a standard cortisol infusion (1 mg /kg) and certain of its degradation products in an attempt to determine whether or not there was diminished conjugation of 17 hydroxycorticosteroids in the presence of a suitable substrate and to deduce the metabolic pathway of cortisol degradation

The rate of removal of free 17 hydroxycorticosteroids from the plasma of patients with liver disease was decreased the half life was 229±19 minutes in cirrhotic patients compared with 112±5 minutes for normal subjects The rate of removal was correlated with the severity of hepatic impairment The levels of conjugated 17 hydroxycorticosteroids in plasma after the infusion were lower in patients with liver disease especially in those with ascites The lower levels in the presence of ascites were attributable to the large distribution volume The apparent impairment of 17 hydroxycorticosteroid conjugation was not observed after infusion of tetrahydrocortisone This was interpreted as evidence that in liver disease there is impairment of reduction of cortisol to its hydrogenated metabolites which are the substrates for conjugation In the presence of suitable substrate conjugation proceeds normally in patients with liver disease After tetrahydrocortisone tetrahydrocortisol and dihydrocortisone were infused into patients with liver disease the rates of removal of free 17 hydroxycorticosteroids from the plasma and the appearance of the conjugated forms were strikingly faster than after infusion of cortisol Thus the defect in pa

(4) J Cl E d 1 17 1395 1406 Dec mbe 1957

tion of this steroid was normal in hypothyroidism and elevated in hyperthyroidism

When a standard infusion of corticotrophin was given to 3 patients with hyperthyroidism free 17 hydroxycorticosteroids rose less and conjugated 17 hydroxycorticosteroids more than in 4 similarly treated hypothyroid patients In 3 of these patients studies were repeated after the BMR was controlled Total output as judged by urinary excretion as directly related to the BMR (Fig 44) Thus an in

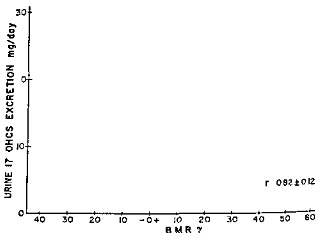


Fig 44 —R l t b tw BMR d 4 h u n y t f 17 hyd t t l p t t w th thy d d b f d aft t tm t (C rte y f B w H t l J Cl E d c h l 18 167 1 9 F b y 19 8)

creased metabolic rate leads to increased conjugation and removal of cortisol from the plasma whereas a decreased metabolic rate has the opposite effect Plasma levels were more influenced by the rate of removal of 17 hydroxycorticosteroids than by adrenal response to corticotrophin

Since conjugation of tetrahydrocortisone appears to be normal in hypothyroidism though the formation of conjugated 17 hydroxycorticosteroids is retarded by administration of cortisol it is probable that hypothyroidism entail a decrease in the reduction of cortisol to substrates suitable for conjugation

Proper assessment of adrenocortical function requires determination of the rate of removal of 17 hydroxycorticoste

duced by spinal anesthesia may delay 17 hydroxycorticosteroid response to the trauma of surgery until the anesthetic has worn off

Urinary Corticosteroid Excretion Patterns in Patients with Adrenocortical Dysfunction were studied by Inge Dyrenfurth Stella Sybulski Vera Notchev J C Beck and Eleanor H Venning[6] (McGill Univ) The patterns in normal subjects showed the presence of pregnane 3α 11β 17α 21 tetrol 20 one (THF) pregnane 3α 17α,21 triol 11 20 dione (THE) cortisol (compound F) cortisone (compound E) and 5 unidentified compounds X_1 X_6 X_9 X_{10} and X_{11} In addition corticosterone (compound B) was excreted by 1 patient and pregnane 3α 11β 21 triol 20-one (THB) in 2 normal subjects Compound THE and THF were the chief metabolites

In 3 patients with Cushing s syndrome similar compounds appeared on the paper chromatograms However they were excreted in much larger amounts During administration of corticotrophin all the α ketolic steroids were further increased the greatest rise occurring in the active hormones F and E There was no increase in the amounts of the fast moving compound X_9 and X_{11} After adrenalectomy these substances disappeared from the patterns and compounds X_1 THF THE F E and X_6 were observed as metabolites of the administered cortisone

A patient with panhypopituitarism presented qualitatively a normal distribution of corticosteroids Quantitatively however the amounts of all the individual compounds were decreased and remained unchanged after administration of corticotrophin A patient with Addison s disease showed no α ketolic steroids except for traces of THF and THE in both the untreated state and during administration of corticotrophin

A boy with congenital adrenal hyperplasia had an abnormal excretion pattern He excreted large amounts of pregnane 3α 17α 21 triol 20 one (THS) and smaller amounts of 11 desoxycortisol (compound S) both of which became almost completely suppressed by cortisone therapy A girl 21 with adrenogenital syndrome had a normal pattern of

(6) J Cl E loc 1 18 391 40 Ap 1 1958

tients with liver disease is in transformation of cortisol to reduced 17 hydroxycorticosteroid which can then be readily conjugated This reduction probably depends on an intrahepatic enzyme reaction

Studies in Surgical Endocrinology IV Anesthetic Agents as Stimuli to Change in Corticosteroids and Metabolism William G Hammond Leroy D Vandam John M Davis Rodman D Carter Margaret R Ball and Francis D Moore (Peter Bent Brigham Hosp) found that preoperative apprehension and preanesthetic medication were not associated with elevations of the free blood 17 hydroxycorticosteroids

In a single instance local anesthesia was not associated with alterations in blood levels or urinary excretion of adrenal corticosteroids or with changes in metabolic balance

General anesthesia produced by Pentothal[*] nitrous oxide and d tubocurare in any combination was not associated with significant changes in blood or urinary 17 hydroxycorticoid values nor did such anesthesia produce alterations in sodium potassium or nitrogen balance Operation under such anesthesia was followed by elevation of the free blood 17 hydroxycorticosteroids but the magnitude of the rise was not as great as that seen with operation under ether

Ether and cyclopropane anesthesia were associated with prompt marked and persistent elevations of blood level and urinary excretion of 17 hydroxycorticosteroids and with changes in the metabolic balance of sodium comparable to those previously observed after administration of corticotrophin to the fasting subject No changes in metabolic balance of potassium or nitrogen were seen Ether produced more marked changes than cyclopropane

The characteristic rise of free blood 17 hydroxycorticosteroids was seen only when ether anesthesia was maintained in the upper planes of stage III for at least 1 hour or in plane three for 15 minutes or more

Operation after held anesthesia with ether produced high levels of free blood 17 hydroxycorticosteroids than after that with Pentothal[*] nitrous oxide and d tubocurare anesthesia

Sensory afferent denervation of the operative site a pro-

(5) Ann Surg 148 199 11 August 1958

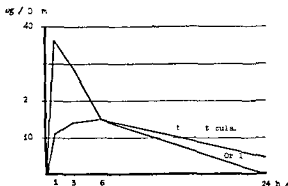


Fig 4 —Me n h g n l l f f e pl m 17 h dr y rt st l ft l d t a rt cul adm t t m f 50 mg hyd c rt son a t t ((rt y f Okla M J Ll F d c 1 18 55 763 J l 19 8)

in plasma levels was influenced by the dose injected It is therefore easy to understand how systemic hormonal effects —improvement in involved joints not treated by steroid in jection and changes in sugar metabolism—have been ob served after intra articular use of hydrocortisone acetate

Enzymatic Basis for Gluconeogenic Action of Hydrocor tisone In the cour e of studies on the effect of hydrocorti sone on enzymes that require pyridoxal phosphate as a cofactor Fred Rosen Nira K Roberts Louis F Budnick and Charles A Nichol[8] (Roswell Park Mem l Inst Buffalo) noted as much as 500% increa e in the glutamic pyruvic transaminase activity in livers of rats treated with 2 5 or 5 mg hydrocorti one/day Under the same conditions val ues for glutamic oxalacetic transaminase (GOT) were only slightly higher than tho e of untreated controls

Lactic acid dehydrogenase an enzyme that does not re quire pyridoxal phosphate was not affected by treatment with hydrocortisone Similar analyses of whole brain from the same animals revealed less than 20% increase in GPT activity and no significant changes in GOT and lactic acid dehydrogenase values a sociated with treatment Neither depletion of pyridoxine nor administration of this vitamin appears to affect the changes in hepatic GPT levels pro duced by hydrocortisone

(8) S e 1 7 287 98 F t 7 1) 8

corticosteroid excretion After administration of corticotrophin relatively large amounts of THS could be demonstrated in the urine Therapy with 9α fluorohydrocortisone only slightly suppressed the excretion of all the individual corticosteroids

Actions of Corticoids and Corticotrophin

Absorption of Acetates of Hydrocortisone Δ^1-Hydrocortisone and Cortisone from Joint Cavity into Circulation It is well known that intra articularly injected cortisone acetate has little local antirheumatic potency in contrast to that of hydrocortisone acetate After intra articular injection of 50 mg hydrocortisone acetate in 13 patients with rheumatoid arthritis Martti Oka[7] (Helsinki) found a definite rise in the level of free plasma 17 hydroxycorticosteroids in 12 Maximum levels were reached after 3 6 hours and a decrease occurred in 12 24 hours Intra articular injection of 100 mg in 7 patients caused a marked elevation in the free plasma concentrations in each The plasma conjugated 17 hydroxy *corticosteroids rose slowly reaching a peak in most* after 24 hours

Absorption of orally ingested hydrocortisone acetate into the circulation was more rapid and greater than absorption from intra articular injections as shown by a comparative study on 6 patients After 24 hours 17 hydroxycorticosteroids were still circulating in 5 of the patients given hydrocortisone intra articularly but in none of those to whom it had been given orally (Fig 45)

It has been shown previously that intra articularly injected hydrocortisone cortisone and their acetates disappear rapidly from the joint cavity According to one report 85 and 98% of the injected steroids had disappeared after 1 and 3 hours *respectively Metabolite formation in the synovial* cavity was also observed To a great extent this rapid disappearance appears to be caused by absorption from the synovial cavity into the circulation In the present investigation all three steroids studied hydrocortisone Δ^1 hydrocortisone and cortisone appeared in the plasma in significant quantities 3 6 hours after intra articular injection The rise

(7) J Cl E d c I 18 55 63 J ly 1958

Mechanism of Glucosuria Produced by Administration of Steroids with Glucocorticoid Activity Routine methods for measuring glucose in urine depend on its reducing properties or its effect on a plane of polarized light Daily excretion of glucose is normally estimated to be 1 Gm However only a small percentage of this substance is actually glucose By use of a specific and simple enzymatic method young healthy subjects have been shown to excrete consistently an average of 115 mg glucose daily rarely over 200 mg This rate is relatively independent of variations in the dietary carbohydrate intake The acute administration of carbohydrate active steroids however almost invariably increases glucose excretion In most normal subjects this augmented glucosuria does not exceed 3 Gm but in patients with diabetes it may reach 100-150 Gm

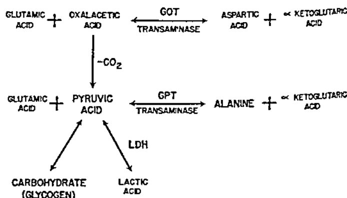
To investigate the mechanism by which increased glucosuria is produced E Rudolph Froesch Albert I Winegrad Albert E Renold and George W Thorn[9] (Harvard Med School) carried out glucose titration studies in normal subjects on control days and during administration of prednisone Administration of the steroid led to increased glucosuria in all instances This effect was greater after 12 hours than after 4 days of prednisone action Glomerular filtration rate was increased over the individual control values in 5 of 6 studies during prednisone administration Decreased glucose tolerance was observed in all subjects 12 hours after the beginning of prednisone therapy but returned to or toward normal on the 4th day of administration In no instance was there a significant decrease in the maximal rate of glucose reabsorption capacity nor did significantly increased glucosuria occur at glucose loads below maximal reabsorption capacity In two patients with Cushing's syndrome and steroid diabetes the maximal glucose reabsorption capacity was normal Impaired glucose tolerance and/or increased glomerular filtration rates adequately explained the excess glucosuria observed during prednisone administration

Two patients with renal glucosuria and measurable urinary glucose excretion at fasting blood glucose level were given intravenous infusion of cortisol over 10 hours during prolonged fast Blood glucose increased markedly in both

(9) J Cl I t 37 5 4 5 A 1 19 8

Daily subcutaneous injection of rats with 2.5 mg prednisone or 5 mg cortisone acetate for 1 week resulted in more than a fivefold increase in liver GPT activity in each case. In a comparable experiment in which 3 mg desoxycorticosterone was administered daily, hepatic GPT values were not increased and appeared to be somewhat lower than those of untreated controls.

Of the many amino acids which have been studied for gluconeogenic activity, alanine, aspartic and glutamic are unique with regard to high gluconeogenic potency. Relation between substrates in the transaminase reactions stud-



F'g 46—T m n se ct on d p thw t brh d at thesı (Cou v f Rosen F t l S 1 8 8 Feb 7 1958)

ied and the pathway to carbohydrate synthesis is shown in Figure 46. Pyruvic acid appears to be the common intermediate in conversion of these amino acids to glycogen. Both pyruvic and lactic acid are readily converted to carbohydrate and both metabolites occur in elevated concentrations in the blood of patients with Cushing's syndrome and in persons receiving glucocorticosteroids.

These facts plus the observation that a substantial rise in hepatic GPT occurs in rats treated with hydrocortisone in contrast to treatment with desoxycorticosterone strongly suggest that control of hepatic levels of GPT by glucocorticosteroids is importantly related to the mechanism whereby these compounds exert their gluconeogenic activity.

tercurrent distribution and these fractions were al o stud ied The beta fraction was not available as such but was represented by corticotrophin A Ketogenic activity was judged by the increase in blood ketone levels in intact fasting rats 3½ hours after intraperitoneal injection of the test material Light Nembutal® or no anesthesia was used

Oxycel absorbed corticotrophin corticotrophin A and the alpha and gamma fractions had high ketogenic activity Protein corticotrophin and the delta fraction had little or none Boiling with 0 1N sodium hydroxide destroyed the ketogenic activity and ascorbic acid depleting potency but not melanophore stimulating hormone (MSH) activity It is known that this hydrolysis progressively removes the three terminal amino acid The MSH like portion of the molecule remains intact (Fig 17) Pepsin digestion of corticotrophin A *yielded fractions with unimpaired corticotrophin and* MSH activity but reduced ketogenic effect Chymotrypsin destroyed all biologic activity

Since it has been reported that the N terminal end of the beta corticotrophin molecule is essential for its ascorbic acid depleting effect the same structures seem to be involved in the ketogenic effect which should therefore be considered an attribute of the corticotrophin molecule Both corticotrophin and MSH may be reversibly inactivated by oxidation with hydrogen peroxide and reduction with cysteine The ketogenic activity behaves similarly That MSH does not itself have any keto enic power again suggests that corticotrophin is the ketogenic agent

ADDISON S DISEASE

Chronic *Primary Adrenal Insufficiency* *J De Cock J De* Graeff D Smeenk and A Querido (Leiden) pre ent a review of 21 patients (12 females) aged 15 66 who had symptoms of adrenal insufficiency for 1 month to 2 3 years before diagnosis made on the basis of characteristic clinical and laboratory findings The cause of adrenal insufficiency was tuberculosis in 9 metastatic carcinoma in 1 and probable adrenal atrophy in 11 Three of the 11 were members of the same family which had also contained 2 others with Addi

( ) Ned 1 tjd h g k 101 4 6 437 D 1 19 7

and urinary glucose excretion increased from 10 to 35 mg/minute and from 4 to 52 mg/minute respectively. The simultaneous increase in both urine and blood glucose levels *during cortisol administration and during fasting* suggests an increased rate of hepatic gluconeogenesis. Increased glomerular filtration contributed to the increased urinary glucose excretion. Tubular glucose reabsorption was not significantly altered.

Ketogenic Activity of Corticotrophin Presumed Extraadrenal Action since it has been observed in adrenalectomized animals was studied by Frank L. Engel and Mildred G. Engel[1] (Duke Univ.). They revise their previously published opinion that the ketogenic activity is not ascribable to corticotrophin per se. Protein corticotrophin and oxycel absorbed corticotrophin were used. The latter had been subdivided into alpha, beta, gamma and delta fractions by coun

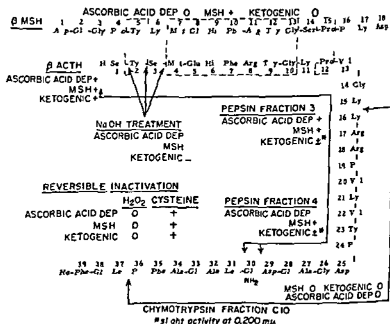


Fig 47—Str ct f bet t t ph d b t MSH n t t t f l g a t ties (Court y f E g l, F L. d E g l M G F doc l gy 6 150 158 F bru y 1958)

(1) Endoc n l gy 6 150 158 Febru y 1958

tercurrent distribution and these fractions were also studied. The beta fraction was not available as such but was represented by corticotrophin A. Ketogenic activity was *judged by the increase in blood ketone levels in intact fasting* rats 3½ hours after intraperitoneal injection of the test material. Light Nembutal® or no anesthesia was used.

Oxycel absorbed corticotrophin, corticotrophin A and the alpha and gamma fractions had high ketogenic activity. *Protein corticotrophin and the delta fraction had little or none.* Boiling with 0.1N sodium hydroxide destroyed the ketogenic activity and ascorbic acid-depleting potency but not melanophore stimulating hormone (MSH) activity. It is known that this hydrolysis progressively removes the three *terminal amino acids. The MSH like portion of the molecule* remains intact (Fig. 47). Pepsin digestion of corticotrophin A yielded fractions with unimpaired corticotrophin and MSH activity but reduced ketogenic effect. Chymotrypsin destroyed all biologic activity.

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Addison's Disease

Chronic Primary Adrenal Insufficiency. *J. De Cock, J. De Graeff, D. Smeenk and A. Querido (Leiden)* present a review of 21 patients (12 females) aged 15-66 who had symptoms of adrenal insufficiency for 1 month to 2 3 years before diagnosis made on the basis of characteristic clinical and laboratory *finding.* The cause of adrenal insufficiency was tuberculosis in 9, metastatic carcinoma in 1 and probable adrenal atrophy in 11. Three of the 11 were members of the same family which had also contained 2 other with Addis

(2) Nederl. tijdsch. geneesk. 101: 416-417, Dec. 1, 19

son's disease. The 3 included in the series were a girl 15 with a father who had died of Addison's disease, her paternal aunt 36 who died in addisonian crisis following child birth, and a female cousin of the latter 21. An aunt of the last 2 patients had had darkly pigmented skin and had died at 65. The mother of the second patient and the father of the third were brother and sister. In 2 patients adrenal insufficiency was associated with hyperthyroidism and in 1 with hypothyroidism. One patient also had pernicious anemia.

Fatigue is often the principal symptom mentioned by the patient but its significance is not always easy to evaluate. Attention should be given to it if the patient is tired on awakening and fatigue lasts throughout the day. Appearance of nausea and vomiting in a patient with Addison's disease is indicative of impending crisis. Hyponatremia and hyperkalemia are relatively rare except in crises but these changes may also be absent during crises.

Three patients died in crises before cortisone was available. Since the advent of cortisone no deaths occurred during crises. Treatment of Addison's disease includes substitution therapy with cortisone and desoxycorticosterone acetate (DCA), early recognition and treatment of crises and treatment of the primary disease, e.g., tuberculosis. Dosage of DCA and cortisone is regulated by individual indications. With signs of impending crisis and at times of excessive stress (infections, operations, etc.) cortisone dosage should be increased to at least 100 mg. daily.

Until a few years ago the only adrenal steroids regarded as important were the so-called glycocorticosteroids cortisone and cortisol (hydrocortisone) and some steroids from the androgen fraction. Some workers mistakenly regarded synthetic DCA, which never is found in biologically active amounts in the adrenal cortex, as the natural (physiologic) mineral corticoid.

Discovery of aldosterone brought some change, but information on secretion of aldosterone in adrenal insufficiency is still insufficient, though some reports indicate very low or absent activity. Recently some cases of hypoaldosteronism without other disturbances in adrenal function were reported. It seems probable that various types of adrenal deficiency will be differentiated and that the classic picture de-

scribed by Addison will be regarded as only the outward manifestation of the disease

Disappearance of Diurnal Rhythm of Diuresis and Urinary Potassium in Eight Cases of Adrenal Insufficiency Three patients with primary Addison's disease and 5 with functional insufficiency due to hypopituitarism were studied by F Azerad J Ghata and A Reinberg.[3] The patients rested in bed and received a relatively consistent diet in 4 meals at 8, 12, 4 and 8 o'clock. Urinary collections were made every 4 hours and quantitative estimations of potassium, sodium, chloride and creatinine were made on each specimen. Results for each 4 hour period were expressed as percentage of total 24 hour elimination.

The 21 healthy adult controls showed a cyclic rhythm of urinary excretion, i.e., nocturnal diminution of diuresis with a minimum in the early hours between 4 and 8 and a diurnal increase with a maximum at 1-4 (principally in autumn) or 4-8 (in spring). Maximal excretion in the normal subject was twice as much or more as minimal excretion. Potassium excretion showed a similar rhythm with minimal elimination from midnight to 4 and maximal at 8-12 in autumn and 4-8 in spring. Ratio of maximum to minimum was 3:1 or more.

Such rhythms were lacking in patients with organic or functional adrenal insufficiency. Maximal and minimal diuresis were noted but the rhythm varied from the normal and individually in different patients and differences between maximal and minimal excretion were less. Potassium excretion showed similar deviations from the normal curve (Fig 48) and tended to become equalized. Elimination of sodium and chloride in adrenal insufficiency also showed disappearance of normal rhythms.

Administration of 50 mg. corti one by mouth to the 3 patients with primary adrenal insufficiency resulted in cyclic variation of diuresis and of chloride and potassium excretion with a maximum at the 4th to 8th hours and a minimum at the 20th to 24th hours after administration of the hormone. Administration of an almost identical amount (45 mg.) divided into 3 doses at 4 hour intervals to 2 of these patients did not have the same effect and variations in the excretion

(3) [illegible] Soc. m [illegible] 18 484 [illegible] 1957

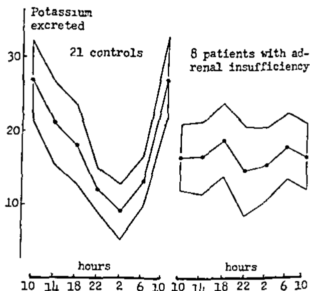


Fig 48 D al to of pot s m t n P t m c et d by k d y du g 4 hou pe d e ſ ed n p c nt f t t l pot m t d 4 h u F m pa t d the f e ch a g f t m s its st da d e r h b n po t d w th cc y of 90% (C u t y f i r d E t l A e Ex l 18 484 491 J ly A g 19 7)

of water and electrolytes were found to be insignificant

The authors conclude that (1) absence of diurnal rhythm in adrenal insufficiency may be interpreted as favoring the diagnosis (2) complete collection of urine throughout the 24 hours is essential for this biologic determination and (3) it may be interesting in some cases to take account of the hour of administration of cortical hormones or of corticotrophin either to re create a nonexistent rhythm in adrenal insufficiency or to leave it undisturbed in a normal subject

Addison s Disease Occurring in Sisters is reported by P H Hewitt[4] making the eleventh family recorded in the literature in which this disease was probably present in more than one member One sister had typical signs and symptoms and has been successfully maintained on cortisone and salt The other was admitted to the hospital in an addisonian crisis and died the next day Autopsy showed that the adrenal cortical tissue was greatly reduced in amount and in some area

(4) B t M J 2 1530 1531 D 28 1957

was absent In the residual cortex zonal architecture was lost The cells were few in number but of giant size owing to cytoplasmic increase Many showed recent degenerative changes No tuberculous reaction was present and there was no fibrosis The medullary substance was normal in amount and appearance In view of the pathologic findings in the patient who died the adrenal lesion in both was considered to be simple atrophy The essential finding in all autopsy records of the previously reported cases was atrophy of the adrenal cortex

► [Five years ago my European friends were amazed at the high frequency of idiopathic atrophy of the adrenal in the United States Most of the European cases reported at that time were associated with tuberculosis It is noteworthy that the incidence of the idiopathic disease is constantly increasing The similarity between the pathologic and clinical processes in this condition and in idiopathic myxedema which now appears to be associated frequently with antibodies to thyroglobulin suggests the possibility of an autoimmune mechanism in spontaneous Addison's disease —Ed]

Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17 Hydroxycorticoids Diagnostic Implications Najib Abu Haydar Jacques K St Marc William J Keddy John C Laidlaw and George W Thorn[5] (Boston) observed 7 patients with some stigmas of Addison's disease but with normal basal level of 17 hydroxycorticoid excretion in the urine None of the patients responded to corticotrophin with a rise in steroid excretion thus demonstrating the absence of significant adrenocortical reserve In 6 patients the first symptom was hyperpigmentation most prominent in exposed areas extensor surfaces pressure points skin folds scars and mucous membranes Weakness was present in 5 and 2 showed weight loss 2 hypoglycemia and 4 water and electrolyte disturbances Severity of symptoms varied widely and could not be correlated with levels of urinary 17 hydroxycorticosteroids Control levels were within normal limits 1 10 mg /24 hours The diurnal pattern of excretion was normal in 2

In all 7 patients 25 units of corticotrophin given intravenously over 8 hours on 2 or more consecutive days failed to elicit the rise in 17 hydroxycorticosteroid excretion that would be expected from a normal adrenal gland although a small initial rise in excretion was noted in 3 Urinary 17

(5) J Clin E[illegible] 18 [illegible] 113 F[illegible] 19[illegible]8

ketosteroid excretion was also normal and did not rise after corticotrophin administration The eosinophil count did not fall as it normally does after administration of corticotrophin Chromatographic analysis of the urine showed the responsible compound to be tetrahydrocortisone a major metabolite of hydrocortisone

Final diagnosis of complete adrenocortical insufficiency rests on the absence of adrenal steroid metabolites in the urine Once this is established response to corticotrophin *differentiates secondary from primary adrenal insufficiency* In the former the defect is at the adrenal level and prolonged administration of corticotrophin fails to elicit a rise in urinary corticoids In the latter prolonged administration of corticotrophin gradually increases corticoid excretion The diagnosis of partial adrenocortical insufficiency likewise depends on evaluating the response to corticotrophin Lack of urinary 17 hydroxycorticoid response after maximal stimulation with corticotrophin despite normal control values is the criterion for such a diagnosis

In the 7 patients adrenocortical insufficiency was partial or compensated Secretion was sufficient to maintain homeostasis under resting conditions but evidence of insufficiency appeared under conditions of stress Early clinical recognition of partial adrenocortical insufficiency is of practical importance because under conditions of severe stress acute *adrenal insufficiency may occur and go unrecognized*

► [Partial Addison s disease has been described previously and more definitively established by serum corticoid level in the report of Nordin (Proc Roy Soc Med 48 1024 1955) and subsequently by Bayliss and by others (1957 58 YEAR BOOK OF ENDOCRINOLOGY p 274) —Ed]

CUSHING S DISEASE AND CUSHING S SYNDROME

► Because of the large number of words involved in the long expression Cushing s syndrome due to adrenal cortical tumor I have substituted the shorter term Cushing s syndrome and for the disease associated with bilateral adrenal cortical hyperplasia originally delineated by Harvey Cushing I have used the term Cushing s disease —Ed

Studies in Cushing s Syndrome I Observations on Response of Plasma 17 Hydrocorticosteroid Levels to Corticotrophin Localization of the lesion in Cushing s syndrome is still disputed Nicholas P Christy Donald Long on and

Joseph W. Jailer[4] (Columbia Univ.) presented data which suggest that the established hyperresponsiveness of the adrenal cortex to corticotrophin in this condition may not be due solely to an intrinsic disorder of that organ but may implicate the anterior pituitary. Previously reported studies demonstrating hyperreactivity of the adrenal cortex to infused exogenous corticotrophin were confirmed in 14 of 1[illegible] patients with Cushing's syndrome. These patients had abnormally elevated levels of circulating 17-hydroxycorticosteroids after intravenous corticotrophin. This probably cannot be ascribed to delayed disposal of cortisol from the plasma. The hyperresponse persisted in 6 patients after unilateral adrenalectomy but it may be abolished if 90-95% of the adrenal tissue is removed surgically. The patients with Cushing's syndrome continued to show excessive response to corticotrophin during prednisone therapy, in sharp contrast to normal persons in whom such treatment suppresses the adrenocortical response to exogenous corticotrophin.

Limited data suggest that in patients with adrenal hyperplasia who experience clinical remission after pituitary irradiation the adrenocortical response to corticotrophin reverts toward normal. In 3 patients who did not improve clinically after pituitary irradiation adrenocortical response remained excessive. Inexplicably, 10 severely ill patients who had no evidence of adrenal cortical hyperplasia also showed excessive plasma 17-hydroxycorticosteroid response to corticotrophin. This merely emphasizes the fact that such a hyperreactivity is not unique in or diagnostic of Cushing's syndrome with bilateral adrenal hyperplasia. In [illegible] 6 patients with Cushing's syndrome associated with adrenal cortical adenoma or carcinoma such hyperreactivity did not occur.

Interpretation of existing evidence varies considerably. They imply either an adrenal or a pituitary origin of the hyperplasia or possibly a hypophyseal corticotrophin potentiating factor which operates on the adrenal cortex. A unifying hypothesis for the many discordant observations is needed.

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(4) Am. J. Med. [illegible] December [illegible]

Effect of Prednisone on Adrenal Responsiveness to Corticotrophin in Normal Subjects and in Patients with Treated and Untreated Cushing's Syndrome Recent studies have shown that daily administration of 30 50 mg prednisone for 7 days to normal subjects suppresses the adrenocortical response to corticotrophin as measured by plasma levels of 17 hydroxycorticoid This response is attributed to inhibition of elaboration or release of corticotrophin by prednisone Patients who have bilateral adrenocortical hyperfunction fail to respond this way to prednisone Jack Geller Agustin S Alvarez Aron Gutman Atilo de Freitas J Lester Gabrilove and Louis J Soffer (Mount Sinai Hosp New York) evaluated the results of this test in patients with Cushing's syndrome before treatment and during partial or complete clinical remission after pituitary irradiation with or without unilateral adrenalectomy

Patients with active Cushing's syndrome not due to tumor showed no suppression of response to corticotrophin administration after 7 days of prednisone therapy Of 4 patients in complete clinical remission as measured by clinical and laboratory criteria including normal levels of plasma and urinary 17 hydroxycorticoids 2 still responded abnormally to the prednisone test in that they showed an adrenocortical response to corticotrophin after 7 days of prednisone therapy In the other 2 results of the test were normal Of 3 other patients in only partial remission 2 had a persistently abnormal response to the prednisone test

The fact that patients in remission with neither clinical nor laboratory evidence of Cushing's syndrome may still show an abnormal response to corticotrophin after administration of prednisone suggests that this abnormality may be used as an additional aid in the diagnosis of adrenocortical hyperfunction

► [This report makes an important contribution to our knowledge of the pathogenesis of Cushing's disease and it is noteworthy that it emanates from the same group who first described the hyperreactivity of the adrenal cortex to administration of corticotrophin That the stimulated gland was not suppressed by administered corticoids strongly suggests an adrenal cortical autonomy such as has been described for the thyroid in Graves disease by Werner and amply confirmed by many subsequent studies —Ed]

Stimulation and Suppression of Adrenal Cortex in Cushing's Syndrome has been advocated by many authors as a

J Clin Endoc 18 409-416 April 1958

biochemical means for differentiation of the underlying pathogenetic mechanism J D N Nabarro Audrey Moxham and G Walker[8] (Middlesex Hosp London) report results of stimulation tests performed on 26 patients with normal adrenal function 23 hirsute women 13 patients with

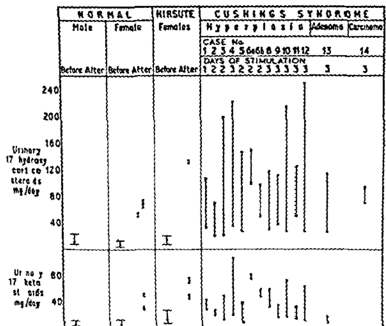


Fig 49—Cortcotrophin stimulation test … (Courtesy of Nabarro J D N et al J Clin Endocrinol 18 586 599 June 1958)

Cushing s syndrome (hyperplasia 11 adenoma 1 carcinoma 1) (Fig 49) and 3 patients with hormone secreting adrenocortical carcinoma without Cushing s syndrome and of suppression tests on 11 patients (adrenocortical hyperplasia 9 adenoma 1 carcinoma 1) Stimulation was performed with corticotrophin gel 9α fluorohydrocortisone was used for suppression Response was assessed from changes in urinary 17 hydroxycorticosteroid and 17 ketosteroid excretion

(8) J Cl Endoc n l 18 586 599 Ju 1958

The stimulation tests showed an abnormal increase of urinary 17 hydroxycorticosteroids in 1 obese male 1 normal male 15 hirsute females and 7 of the 11 patients with Cushing s syndrome due to adrenocortical hyperplasia One patient with an adenoma had a moderate increase in urinary 17 hydroxycorticosteroids and 2 patients with adrenal carcinoma without Cushing s syndrome had an increase in steroid excretion on stimulation In the patient with adrenocortical carcinoma that gave rise to Cushing s syndrome only a slight increase occurred in urinary 17 hydroxycorticosteroid

The results in general confirm the findings of previous workers as regards adenomas and carcinoma Response in the patients with Cushing s syndrome due to hyperplasia were variable

The suppression tests indicated that 9α fluorohydrocortisone will reduce urinary steroid excretion in some patients with Cushing s syndrome due to adrenocortical hyperplasia In the suppression tests only 4 of 9 patients with hyperplasia showed a reduction in steroid excretion The patient with adenoma the patient with carcinoma and the other 5 patients with adrenocortical hyperplasia showed no change Therefore inability to suppress urinary excretion of 17 ketosteroid or 17 hydroxycorticosteroid is not definite evidence of tumor A positive suppression test strongly favors hyperplasia but absence of suppression does not exclude it

Response to stimulation or suppression test was not shown to be related to the likelihood of relapse after subtotal adrenalectomy After diagnosis of Cushing s syndrome is established it is extremely doubtful whether biochemical or radiologic investigations are justified in an attempt to find the underlying cause

► [Cushing s disease and Cushing s syndrome are relatively rare and even the largest clinical centers have comparatively few cases for study In addition since the diagnostic criteria vary considerably from place to place a diagnosis *made by any one set of investigators is not necessarily* accepted elsewhere Consequently generalizations regarding the suppressibility of the adrenal cortex in Cushing s disease have been based on relatively few studies Suppression of the cortex is apparently a variable response and as Nabarro and co workers suggest should not be the basis for definitive diagnosis —Ed]

Test of Corticoadrenal *Inhibition by Means of 9α fluoro Δ1 cortisol* Critical Study was made by L de Genne H

Bricaire L Moreau and B Mathieu de Fossey[9] (Paris) On 7 patients with minor functional hypercorticism 3 with Cushing's syndrome due to surgically verified adrenocortical hyperplasia and 4 controls The synthetic hormone (Δ_1 FF) was given as follows 2 mg/24 hours the first 2 days increased to 4 mg/24 hours for 2 or 3 days The test was carried out for a minimum of 4 days

In definitely active Cushing's syndrome the dose was 4 mg/24 hours the first 2 days increased to 6 mg the 3d day Estimations of 17 ketosteroids (Zimmermann) and 17 OH (Porter Silber) were made for 2 days before during and 2 days after withdrawal

In the 4 controls secretion of 17 OH decreased below 2 mg/24 hours the 2d day and below 1 mg the 3d and 4th days indicating almost complete suppression of adrenal secretion That the level of 17 ketosteroids did not go below 4 mg/24 hours even in the one woman demonstrates that androgens in both sexes are of mixed gonadal and adrenal origin In 3 of the controls return of endogenous adrenal secretion was noted 24 hours after withdrawal of the hormone in the other after 48 hours

The 7 patients with functional hypercorticism gave essentially the same response as the controls to the inhibition test These results removed all suspicion of tumor or adrenocortical adenoma and in cases of hypertrichosis served as a guide to therapy with corticoids of delta cortisone type to block production of adrenal androgens

The 3 women with major hypercorticism (Cushing's syndrome) who had bilateral adrenalectomy all showed histologically verified cortical hyperplasia with no tumor One showed an adenomatous reaction Though theoretically the inhibition test should be positive in these 3 patients only 1 responded to Δ_1 FF In the second patient the response was doubtful and could not be interpreted and in the third the response remained completely negative

In differentiation between adrenal hyperplasia and tumor —the hypothetical value of the inhibition test—the test proved definitely unreliable though it was carried out with a very potent glycocorticoid in triple the dose that normally block cortical secretion

(9) I ... 66 1783 1 86 ... 15 1958

The authors believe as do other workers who have experimented with it that the inhibition test may have some value as a therapeutic guide rather than as a diagnostic method In minor *virilizing hypercorticism definite* decrease in the level of androgens by Δ_1 FF would suggest the value of prolonged treatment with delta cortisone Experience has shown that true Cushing s syndrome does not respond to treatment by inhibition

Cushing s Syndrome in 18 Month Old Girl Cured after Removal of Adrenocortical Adenoma H Krauss and H G Kraimick[1] (Univ of Freiburg) report a case

Girl aged 18 months was hospitalized because of increasing over weight (Fig 50) onset of which could be traced back to early infancy She presented the over all appearance of Cushing s syndrome *with* certain exceptions Virilization was manifested by scant pubic hair bean sized clitoris and a six to eightfold increase in urinary 17 ketosteroids Growth and bone and dental development were normal for the child s age probably as a result of the anabolic effect of the androgens Probably *for similar reasons* there was *no* osteoporosis A hemogram showed polycythemia lymphopenia leukocytosis and a shift to the left

Blood pressure was 165/115 mm Hg Glucose tolerance was reduced considerably Tomograms after retroperitoneal air insufflation revealed a tumor in the area of the right adrenal gland (Fig 51)

Before surgery corticotrophin cortisone and desoxycorticosterone acetate were given the corticotrophin for stimulation of the contra lateral adrenal which is often atrophic in adrenal tumors At surgery *an adrenal tumor well* encapsulated measured *4×3 5×3 5 cm* Histologically it proved to be an adenoma The child tolerated the operation well but blood pressure remained high and occasionally rose to 240/160 It could be decreased temporarily with Regitine® Repeated urinary assays revealed no vasopressor agents During the 5th postoperative week the blood pressure fell spontaneously and remained about 105/65 A week later bilateral papilledema and dehiscence of the cranial sutures were noted Both regressed in a few weeks

After weight loss and development of normal body proportions occurred the Cushing s syndrome gradually subsided and *the child re* gained her individuality in appearance and behavior The signs of the concomitant androgenic syndrome regressed slowly Only after 21 months (Fig 52) did the pubic hair disappear The clitoris remained *enlarged*

Before operation the 24 hour urinary excretion of corticosteroids was 1 600 µg (normal 200 300 µg by the method of Stasadinger and Schmeisser) and of 17 ketosteroids 5 9 mg Two months after operation the values were 440 µg and 1 2 mg During a 4 year follow up the child developed normally

(1) Deutsche med Wchnschr 83 321 3 4 Feb 8 1958







Fig 50 (bo l (t) —Ch ld t f x)
Fig 51 (bo) P l t g m w th t h l w h l w l
Fig 5 (l ft) Ch ld l m th f s
(C t y f k a H l K n k H t D t be n f W h b 93 3 1 3 4 F l 9 1959)

The pure form of Cushing's syndrome is rare in childhood and is usually accompanied by signs of virilization due to androgen production by the adrenal tumor

Roentgenologic Changes of Skeletal System in Cushing's Syndrome were studied in lateral spinal views in 69 patients by Willard J Howland Jr David G Pugh and Randall G Sprague (Mayo Clinic and Found) Roentgenologic evi

(2) Radiology 71 69 8 July 1958

dence of osteoporosis was present in 68 and was about equally severe in the spinal column pelvis and ribs Osteoporosis of the extremities was less severe and was occasionally absent About 40% of the skull roentgenograms showed an irregular metastatic type of decalcification Sellar enlargement was present in 7 of 43 instances Decreased osteoporosis of the skull associated with clinical remission after



F g 53 (left) —Ma g l de at p e t n t th a c t b wom n 49 w th ympt ms f d oc t l h p f t on for 4 y b t w th b k p n
F g 54 (e t) —Not m g nal d at on f d a d 3d l m l a t b e t th r p t t
I g 55 (r ght) —S me p t nt 10 m th l te d t h d rp ed n the 9 months s t tm nt
(C rte y of Howl d W J *et* *l* R d logy 71 69 78 J ly 1958)

adrenalectomy was noted in 8 of 13 patients Two third of the 69 patients had rib and 6 had pelvic fractures but rarely was a patient aware of these

Marginal condensation of multiple vertebral bodies associated with compression fractures occurred in 29 patients (42% of all patients 55% of those with moderate or severe osteoporosis) and involved principally the lower thoracic and upper lumbar regions In 8 of 18 instances roentgenograms made after remission showed improvement in spinal

osteoporosis For 8 patients in whom spinal roentgenograms showed marginal condensation posttreatment roentgenograms were available The condensation had remained unchanged in 2 (Fig 53) and had decreased or disappeared in 6 (Figs 54 and 55) Disappearance of zones of condensation may be the first roentgen sign of improvement of the disordered osseous metabolism

Review of the records and roentgenograms in 50 control with severe osteoporosis not associated with Cushing's syndrome disclosed no painless fractures or abnormal fracture calluses There was only one instance of minimal marginal condensation of a vertebral body

Thus marginal condensation of vertebral bodies may often be associated with vertebral fractures in Cushing's syndrome but rarely seen in other forms of osteoporosis Multiple painless fractures of ribs and pelvis appear to be a differential feature of this disease

Vertebral condensation and abnormally large fracture callus in the ribs and pelvis reflect the abnormal healing of fractures of osteoporotic bone in Cushing's syndrome These features and the osteoporosis itself improve in a significant proportion of cases when adrenocortical secretions are decreased by adrenalectomy or excision of an adrenocortical tumor Vertebral compression with marginal condensation or painless fractures of the ribs or pelvis should suggest possibility of Cushing's syndrome

► [The distribution of the bones affected by Cushing's disease and Cushing's syndrome is particularly interesting Unlike the more common postmenopausal osteoporosis Cushing's disease frequently results in fractures of rib and radiolucency of the long bones Involvement of the vertebrae is common in both I have never seen the eburnation of the thoracic vertebrae described here Unlike the situation in menopausal osteoporosis the skeletal lesions of Cushing's disease heal after correction of the underlying endocrine defect The peculiar nature of the healing has led to a recent exchange of correspondence in the *Journal of Clinical Endocrinology and Metabolism* by Moldawer (18 1028 1958) and Howard (p 1131) —Ed]

Occurrence of Allergic Disease in Patients with Cushing's Syndrome Haddon M Carryer and Archie W Miller[3] (Mayo Clinic and Found) studied 101 patients with Cushing's syndrome 19 of whom had adrenal cortical tumors (5 malignant) and 82 adrenal cortical hyperplasia All were

(3) J All gy 9 435 49 N mb 1958

treated by subtotal or total adrenalectomy Of the 101 patients 8 had a history of allergic disease Drug allergie occurred in 6 and 2 had a history of asthma and hay fever Striking remissions of nasal allergic di orders and bronchial asthma were correlated with development of Cushing s syndrome in the 2 patients After surgical extirpation of a major part of the functioning adrenal cortex allergic symptoms recurred A less clear cut relationship was observed concerning drug allergy in the 6 patients

Drug allergy may occur in patients manifesting excessive or deficient adrenal cortical function Allergic reactions occurred before and after adrenalectomy for correction of Cushing s syndrome although large doses of cortisone postoperatively effectively suppressed drug allergy

The authors suggest that defects in the metabolism of adrenal steroids congenital or acquired may be the basis for the so called allergic diathesis

Cushing s Syndrome Produced by Normal Replacement Doses of Cortisone in Patient with Defective Mechanism for Steroid Degradation Endocrine disorders are usually considered in terms of over or underproduction of a hormone or as iatrogenic due to excessive quantities of one or more compounds Seldom is the possibility considered of disorders in the mechanisms of destruction inactivation or excretion of a hormone John Eager Howard and Claude J Migeon[4] (Johns Hopkins Univ) report a case which they consider an example of this type of disturbance

Man 43 had hypophysectomy for acromegaly 5 years previously followed 3 years later by classic panhypopituitarism Steroid levels were low and the glucose tolerance curve was flat At that time he had a 1 1 albumin globulin ratio and a 4+ cephalin flocculation reaction He was started on 30 mg methyltestosterone daily and 25 mg cortisone orally in divided doses which resulted in dramatic improvement After 2 years of treatment he complained of severe morning headaches He weighed 200 lb and the face and neck were fat but the arms and legs thin Striae were broad and red over the abdomen Blood pressure was 210/115 The albumin globulin ratio was 1 1 The protein bound iodine level was 1 3 µg /100 ml and rose to 2 8 µg after 3 daily injections of thyroid stimulating hormone With the addition of 2 gr thyroid daily he lost weight appetite decreased and blood pressure fell to 1 0/90 The protein bound iodine level became 6 1 µg Intravenous hydrocortisone 1 mg /kg given over ½ hour

(4) Am J M S 35 38 393 April 1958

demonstrated impaired degradation. Abnormal amounts of hydrocortisone were detected over 6 hours. When the hypothyroidism was corrected the degradation curves returned toward but not to normal.

Corticoids are degraded slowly in hypothyroid states and in hepatic cirrhosis. Both conditions were present in this patient.

In evaluating syndromes due to excessive quantities of a normal hormone the possibility of impaired disposal must be considered. In such cases normal production of a hormone or administration of normal amounts may become physiologically excessive. Perhaps enzymatic or other abnormalities in disposal of hormones may cause some syndromes now called idiopathic.

Cushing's Syndrome: Report of 13 Cases and Their Surgical Treatment. D. A. D. Montgomery and R. B. Welbourn (Belfast) studied 11 females and 2 males with Cushing's syndrome. Average age of onset was 31. Duration of symptoms before treatment averaged 3 years 8 months. All had hypertension which was severe in 3; 3 had severe osteoporosis; 4 had hypokalemic alkalosis; 6 had muscular wasting of the limbs, and in 10 purple cutaneous striae were found. Menstrual irregularities were present in all 8 females who had normal menses before onset of symptoms. Changes in hair growth and in texture and color of the hair were common. Three had infections; half of the patients had polycythemia and in 4 occasional glycosuria and slight elevation of the blood sugar curve were found. Gastric secretion was increased in most of the 9 patients tested. The excretion of reducing corticoids, 17-hydroxycorticoids and 17-ketogenic steroids was increased in most patients.

Most patients were studied by retroperitoneal insufflation of oxygen introduced by the presacral route combined with intravenous pyelography and tomography. The adrenals were usually outlined but it was not possible to detect minor hyperplasia.

Surgical therapy consisted of removal of an adenoma of the adrenal in 1 patient and removal of all of one gland and nine tenths of the other in 12 patients with hyperplasia. In none was a tumor located for certain before operation, and exploration was regarded as part of the investigation. The

(5) Brit. J. Surg. 45:137-15[?], Sept. [?] 1957.

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(4) A J M Sc 35 387 393 Ap 1 19 8

were shed in the form of fine dry scales (Fig 26) Biochemical tests of adrenal function showed that although basal secretion was normal or low response to corticotrophin was absent or at best slight in all

Early diagnosis and treatment are of great importance particularly in older patients if crippling cardiovascular complications are to be avoided

Treatment of Cushing s Syndrome with Amphenone Report of Two Cases One with Probable Thymoma the other with severe depression is presented by E Perry McCullagh and Harvey A Tretbar (Cleveland Clinic) In both cases administration of 1,2 bis(p aminophenyl) 2 methylpropanone I dihydrochloride (amphenone) limited the formation of 17 hydroxycorticoids

CASE 1 —Man 39 with Cushing s syndrome and an anterior mediastinal neoplasm treated 2 years before with x rays and [illegible] was hospitalized in a weak chronically ill condition The mass occupied the anterior portion of the superior mediastinum which had a transverse diameter of 8.5 cm There was no encroachment on the lumen of the trachea The right vocal cord was paralyzed and there was slight generalized demineralization of the dorsolumbar spine weakness of the extremities and slight tremor of the hand X ray gram and presacral air insufflation studies indicated bilateral enlargement of the adrenals A malignant epithelial neoplasm and [illegible] lymph node biopsy was considered to be probably thymic in origin The serum potassium level was 2.9 mEq/l and the ECG showed evidence of hypokalemia Despite oral potassium chloride weakness became more marked Cardiac symptoms were relieved by 80 ml [illegible] potassium chloride given intravenously in addition to the oral [illegible] of 60 ml q daily

A daily [illegible] of 45 units of NPH and 10 units of regular insulin maintained near normal blood sugar level [illegible] amphenone was administered [illegible] 1 Gm /hour for 5 hours on the 10th day Thereafter amphenone [illegible] given orally every 1½ 3 hours for [illegible] days Insulin was [illegible] The effect of this treatment on blood sugar and [illegible] steroid [illegible] and excretion is shown in Figure 57 [illegible] therapy [illegible] 48 hours before bilateral total adrenalectomy During [illegible] the [illegible] pressure varied from 100 to 180 [illegible] Hg [illegible] at the end of operation laryngeal edema required tracheotomy [illegible] the patient died 1 hour later while receiving hydrocortisone and [illegible] intravenously

CASE 2 —A man 41 with Cushing s syndrome was treated by [illegible] of the pituitary 1 year before readmission which led to temporary relief [illegible] followed by exacerbation and development of agitation

61 J Clin Endocrinol 19 134 148 Feb 1959

adrenals were exposed through the flank in two separate operations. All patients were given cortisone and desoxycorticosterone acetate before and after adrenalectomy. About 11 days after operation cortisone was withdrawn slowly, the necessary dosage being determined by absence of signs of adrenal failure when trial reductions were made. Acute peripheral circulatory failure developed within 36 hours of



Fg 56 S ly d q m t f k p t p t ly w m 34 (C rt f M tg ry D A D d W H R H B t J S g 45 13 15 S pt mt 19 7)

operation in 5 patients, 1 of whom died. Acute salt deficiency occurred in 1 patient. Two patients died within 6 months of operation of unrelated causes, although 1 may have had acute adrenal insufficiency. Remission occurred in the 10 patients who survived between 1½ and 4 years. None showed any sign of recurrence. Five stopped taking cortisone and are in good health without it. A sign of improvement and one regarded as an index of adequate and successful operation was a striking change in the skin. It became dry, erythematous and itchy, and the superficial layers

and depression She was given tranquilizing and antihypertensive agents without success

During 8 hours 9 25 Gm amphenone was given intravenously The patient became drowsy relaxed and less depressed for about 20 hours Mild vomiting and nausea occurred Oral treatment with amphenone 0 5 Gm every 4 hours for 3½ days was begun 7 days after the infusion Right total and left subtotal adrenalectomy leaving an estimated 2 3 Gm tissue was then performed Intramuscular and intravenous hydrocortisone were needed for 72 hours to control weakness and hypotension The mental condition improved for 6 days then depression and agitation became so severe as to require electroconvulsive therapy Thereafter hypertension led to reduction of the hydrocortisone dosage and the patient was discharged 40 days postoperatively taking 10 mg hydrocortisone daily

Amphenone acted similarly in these 2 patients with respect to reduction of glucocorticoid formation and of biochemical effects secondary to this formation Urinary 17 ketosteroid levels were reduced during oral therapy but less than corticoids

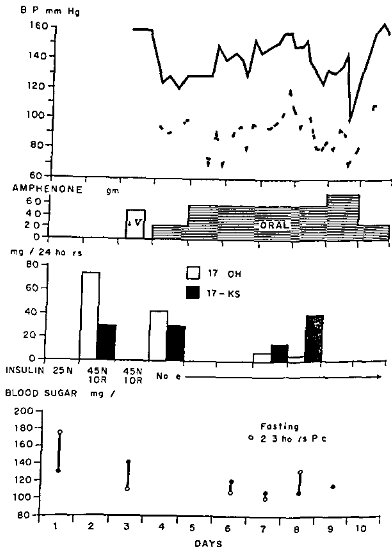
Extra Adrenal Cushing's Syndrome

Hormonal Syndrome of Hyperadrenocorticism with Alkalosis and Hypokalemia Due to Adrenal Metastases from Bronchial Carcinomas is reported in 2 patients by K S Mach P Rentchnick A F Muller J Lagier and H C Plattner[7] (Geneva)

Case 1 —Man 54 previously in good health had persistent bronchitis Six months later he showed weakness and hyperglycosuria and hyperglycemia were discovered They responded poorly to insulin and diet A month later he was hospitalized because of sudden onset of asthenia with generalized muscular weakness and disorientation Except for hepatomegaly clinical examinations showed no significant abnormalities Laboratory studies showed true alkalosis with a pH 7 72 and alkaline reserve 42 mEq blood potassium 2 7 mEq and chloride 80 Gm/L besides diabetes Levels of 17 ketosteroids (21 mg/24 hour) and of urinary corticosteroids were high (9 7 mg/24 hours) The aldosterone level was not determined The patient died 2 weeks after admission Autopsy showed a small undifferentiated carcinoma in the right bronchus massive metastases in the liver and microscopic metastases in both adrenal

Case 2 —Woman 60 with a history of repeated bronchitis that responded to antibiotics had a bronchial lesion diagnosed radiologically a bronchial carcinoma Several days later adenopathy appeared in the left inguinal region with swelling of the left leg Lymph node biopsy showed massive metastasis of solid undifferentiated car

(7) P[illegible] 66 437-438 M[illegible] 12 1[illegible]8



Γᵹ 57 —Effect f amph on blood p u y 17 hyd yc t d f t k t t d f t g a d p t b l blood ga J l a f l q m t (C t y ot M Cull gh E P d T tb H \ J Cl End l 18 134 148 Feb y 1958)

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(7) P m 1 66 437 439 M 12 1958

carcinoma with large clear cells and occasional fusiform cells. Disorientation and hallucinations and somnolence occurred. Laboratory studies showed electrolytic imbalance with metabolic alkalosis, hypokalemia, hypernatremia and hypochloremia. Urinary 17-ketosteroid ranged from 26 to 43 mg/24 hours. Urinary aldosterone was under 1 μg/24 hours. Eosinophils were lacking in all blood counts. A short spontaneous remission coincided with slight clinical improvement, but the patient died in 2 weeks. Autopsy showed bronchial carcinoma with hyperplastic metastases in the liver, kidneys, bones and adrenal that weighed 23 Gm. A large metastatic lesion in the left adrenal and small infiltrations in the right medullar region were noted. Chemical analysis of adrenal tissue showed high levels of cortisol and cortisone and definitely decreased aldosterone levels, corroborating the urinary finding.

Neither patient showed any clinical sign of Cushing's or Conn's syndrome. In Case 1 the humoral disorders and diabetes could be attributed to increased secretion of 17-hydroxycorticosteroid. In Case 2 decreased urinary and adrenal aldosterone level demonstrated that electrolytic disturbances with alkalosis and hypokalemia, an essential element of Conn's syndrome, are not necessarily accompanied by increased production of aldosterone.

Cushing's Syndrome and Bronchogenic Carcinoma. Renato D. Kovach and Laurence H. Kyle[8] (Georgetown Univ.) report a case of this condition and review 6 cases from the literature.

Man, 22, while hospitalized for an apparent respiratory disease, acquired the typical characteristics of Cushing's syndrome, which progressed rapidly. At autopsy the lung showed pulmonary edema, bronchopneumonia and a highly anaplastic (oat cell) bronchogenic carcinoma with metastases to the mediastinal lymph nodes. The adrenals presented a thin atrophic zona glomerulosa and marked hyperplasia of the zona fasciculata. There was one metastatic nodule in the right adrenal cortex, the cells of which were of the same type as those found in the lung.

The clinical pattern of this combination of disorders includes three significant features: (1) weight gain or maintenance of normal weight in the presence of rapidly progressive carcinoma, (2) acute development of features of adrenal hyperfunction and (3) a rapidly fatal course. Hypokalemic hypochloremic alkalosis appears to be a frequent component of this combined disorder, contrasted with its relative rarity in uncomplicated Cushing's syndrome.

The incidence of the association of these two relatively rare

(8) Am. J. M. [illegible] 24 981-988, J[illegible] 1959

diseases appears to exceed mere chance The likelihood of such a rare entity as Cushing s syndrome being associated with bronchogenic carcinoma in at least 7 known cases is highly improbable on the basis of coincidence It seems definitely beyond mere chance that all 7 patients had the same histologic type of carcinoma the anaplastic or oat cell variety The association appears to constitute a distinct syndrome

Cushing s Syndrome Associated with Adenocarcinoma of Ovary is reported by Victor Parsons and Barbara Rigby[9] (King s College Hosp London) Association of Cushing s syndrome with neoplasia in sites such as the thymus bronchus pancreas or ovary has been observed The authors case also shows that the excessively high concentrations of circulating steroid responsible for the clinical syndrome result from oversecretion rather than from failure of inactivation in the liver

Woman 64 with abdominal fulness for 2 months was hospitalized She showed gross ascites and a hard fixed mass high in the left fornix of the vagina External genitalia were normal Blood pressure varied between 190/105 and 170/90 mm Hg A right ovarian mass was excised and deposits of growth were noted in the pouch of Douglas and around the bladder The omentum and liver seemed to be free from deposits The excised mass consisted of ovarian tissue this was the site of a semicystic growth which on section proved to be completely anaplastic except in some area where a poorly differentiated adenocarcinoma was noted

Glycosuria was first noted 3 days after operation The blood sugar level 2 hours after a glucose meal was 334 mg /100 ml Later other facets of Cushing s syndrome—ankle edema purplish petechiae over both legs plethoric facies and hair on the lip and chin—appeared The blood pressure slowly rose to 200/120 Subsequently she received deep x ray therapy to the pelvis Diabetes was controlled with difficulty A urinary infection developed and she died 4 months after the first signs of Cushing s syndrome occurred Output of adrenocortical hormones was high No evidence of failure of hepatic inactivation was noted until the terminal stage

At autopsy the adrenals showed increased thickness of the cortex Sections of the excised ovarian tumor showed an anaplastic carcinoma with no structural features to suggest that it was an arrhenoblastoma or a masculinovoblastoma

The authors assume that the stress of severe and long standing malignant disease might have provoked hyperactivity of the adrenal of sufficient intensity to provoke Cushing s syndrome

(9) L n t 99 994 N 8 1958

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(8) Am J M 1 4 981 988 J 19 8

after injection contained 90% of the administered radioactivity. By the reverse isotope dilution technic, 3α,17α-dihydroxypregnane-11,20-dione, 11-ketopregnane-3α,17α,20α-triol and pregnane-3α,11β,17α,20α-tetrol accounted for less than 0.3% of the radioactivity in the neutral steroid extract of the 24 hour urine after administration. This amount was probably due to trace contaminants.

Hydrocortisone-4-C^{14} administered to a leukemic patient yielded no radioactivity in these compounds when these compounds were added to the neutral steroid extract of the urine during hours 4-6 after administration.

The large amounts of C-21 desoxysteroids present in the urine of patients with congenital adrenal hyperplasia do not arise from hydrocortisone or other C-21 oxygenated hormones. Probably the precursors are C-21 desoxysteroid hormones and these metabolites represent incomplete synthesis of the hormone. Thus there is no reason as yet to alter the current concept of the cause and consequences of this disorder.

Steroid Isolation Studies in Congenital Adrenal Hyperplasia were carried out by David K. Fukushima and T. F. Gallagher[3] (Sloan-Kettering Inst.). The importance of nonketonic metabolites has recently been emphasized by the observation that in man hydrocortisone is metabolized to an appreciable extent to yield completely saturated alcohol such as the cortols or compounds containing only a single unreactive carbonyl group, e.g., the cortolones. Because the existence of other related hydroxylated steroids was suspected an examination of the nonketonic components present in an extract of urine from a patient with congenital adrenal hyperplasia was undertaken.

METHOD.—A 6 day collection of urine from a man with congenital adrenal hyperplasia was treated with beta glucuronidase at pH 5.0 and 37 degrees for 5 days. The urine was adjusted to pH 1.0 and continuously extracted with ether for 48 hours. The neutral fraction was obtained in the usual way. The residual urine and alkaline washes from the initial extract were combined and acidified to 1N sulfuric acid. After continuous ether extraction for 48 hours the neutral fraction was prepared as before. The individual neutral fractions were separated into ketonic and nonketonic fractions by Girard's reagent T and the former was separated into alpha and beta ketosteroid sub-

(3) J. Biol. Chem. [illegible] 9 8 9 [illegible] mb [illegible] 195[illegible]

VIRILIZING HYPERPLASIA

Pregnane 3α 17α 20α Triol and Pregnane 3α 17α 20α Triol 11 One Excretion by Patients with Adrenocortical Dysfunction was studied by K I Cox and M Finkelstein[1] (Univ of Sydney) by chromatography of urine extracts This method which is suitable for routine clinical use permits detection of 100 μg pregnanetriol/24 hours and 50 μg pregnanetriolone/24 hours Excretion of these steroids was determined in 24 normal adults and children 6 patients with adrenocortical hyperplasia before treatment 10 with adrenocortical hyperplasia receiving cortisone prednisolone or similar therapy and 1 with a tumor of adrenal origin

A clear difference was found between normal subjects and *patients with adrenocortical hyperplasia In the latter* pregnanetriolone was excreted in relatively large amounts and there was an associated increase in pregnanetriol levels Pregnanetriolone was not excreted by the patient with a tumor of adrenal origin described here or in 2 cases reported previously *Differentiation* of patients with tumors *of* adrenal origin from those with adrenocortical hyperplasia on the basis of the pregnanetriolone excretion thus seems possible The high levels of pregnanetriol and pregnanetriolone in the urine of patients with adrenal hyperplasia were decreasing during administration of adrenal cortical steroids

Absence of 21 Dehydroxylation in Congenital Adrenal Hyperplasia This abnormality is characterized by inability of the adrenal to complete the synthesis of hydrocortisone *It is a genetically determined inborn error of metabolism* The lesion has been defined as either (1) relative deficiency in introduction of oxygen at C 21 in a 21 carbon substrate or (2) failure of 11 oxygenation with both 21 and 19 carbon substrates

David K Fukushima and T F Gallagher (*Sloan* Kettering Inst) administered hydrocortisone 4 C^{14} intravenously to a patient with congenital adrenal hyperplasia who excreted large amounts of C 21 desoxyhydrocortisone metabolites in the urine The urine collected for 24 hours

(1) J Cl I t 36 17 6 1735 D mbe 19 7
( ) J Cl E d c 1 18 694 698 J ly 19 8

flected by the elevated production of androsterone and etiocholanolone These two compounds are the principal steroids derived from the adrenal androgen By virtue of the increased adrenocorticotrophin secretion resultant from deficiency of hydrocortisone the normal elaboration of the adrenal component is elevated to degree sufficient to produce the masculinization Accordingly the array of C 21 steroid is an expression of the relative inability of the gland to complete the synthesis of hydrocortisone and the elevated androsterone and etiocholanolone excretion are a manifestation of the increased completed synthesis of the adrenal androgen precursor

Familial Congenital Hyperplasia of Adrenal Cortex is reported by G Birke F Diczfalusy L O Plantin H Robbe and A Westman[4] (Stockholm) in a family with 6 children The father mother and 3 children were clinically normal and showed a normal excretion pattern of 17 keto teroid 17 hydroxycorticosteroid and estrogens Tests of corticotrophin could not be made in the normal subjects Of the 3 affected children 1 died at age 6 weeks with appearance of congenital adrenal hyperplasia and adrenal insufficiency Steroidal studies could not be done The other 2 children were female pseudohermaphrodites One had clitoridectomy and bilateral subtotal adrenalectomy in attempt to control the masculinizing symptoms (cortisone in requisite dosage for suppressing adrenocortical secretion gave rise to mental symptoms) The other child was reared as a male

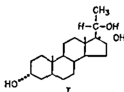
Assays on the 2 patients revealed a partially new steroid excretion pattern characterized by presence of tetrahydro S without hypertension a defect in the 11β hydroxylating mechanism a dichotomy between androsterone and etiocholanolone excretion and a disturbed estrogen pattern There was substantial increase in excretion of 17 ketosteroids and 17 hydroxycorticosteroid Androsterone was predominant in the 17 ketosteroids with little if any etiocholanolone Of the individual 11 oxy 17 ketosteroids 11 ketoandrosterone and 11β hydroxyandrosterone were isolated and indentified by infra red spectroscopy 11 hydroxyetiocholanolone could not be detected Huge amounts of pregnanetriol were found

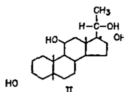
(4) Acta endocr 1 9 55 63 1958

fractions with digitonin A portion of each subfraction was chromatographed on paper

The nonketonic fraction from the enzyme hydrolyzed portion only was submitted to a series of chromatographic separations with use of the partition systems described by Katzenellenbogen and co workers Various eluates were examined by infra red spectrometry

Using this method the authors isolated pregnane 3α 11β 17α 20α tetrol (Fig 58 *II*) and allopregnane 3α 17α 20α triol (*I*) Evidence for presence of allopregnane 3α 17α 20β triol was obtained In addition 22 previously described steroid were isolated and measured The major nonketonic urinary





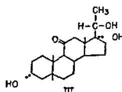


Fig 58 (Courtesy of Fukushima D K and Gallagher T F J Biol Chem 229 9 Nov 1957)

steroids were pregnane 3α 17α 20α triol (65 mg/day) and 11 ketopregnane *3α 17α 20α triol (12 mg/day) (III)* Among the 25 separate steroids found in the patient s urine there was no compound with a C 21 hydroxyl group Thus this patient showed serious deficiency of 21 hydroxylation with excessive excretion of androsterone and etiocholanolone

In another case of congenital adrenal hyperplasia the patient was capable of a high level of C 21 hydroxylation but there was complete absence of C 11 oxygenated steroids together with an androsterone and etiocholanolone output almost the same as that of the present patient

From these examples it can be concluded that the fundamental defect associated with congenital adrenal hyperplasia may be manifest by more than one chemical aberration The virilization associated with this condition is clearly re

The e giantlike and true giant cells have hitherto been observed only in adrenocortical carcinoma and in fetal or newborn adrenal cortex and have been assumed to be carriers of androgenic activity although this cannot be definitely concluded In addition to the presence of these unusual cell the authors were particularly impressed with the nu

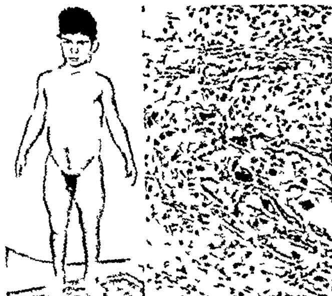


Fig 59 (left) type ... Fig 60 (right) ... [illegible]
(C ... L ... M ... J E ... 10 4 9434 Ap ... 19 8)

merous atavic bodily characteristics Moreover hypertension and cardiac hypertrophy are comparatively rare in androgenic adrenocortical hyperfunction

Simultaneous Occurrence of Female Pseudohermaphroditism and Ovarian Hyperthecosis in Sisters L Feher G Gyory I Less and J Laszlo[5] (Budapest) report on 2 patient with congenital adrenocortical hyperplasia and hyperthecosis of the ovary (Stein Leventhal syndrome)

CASE 1 —Girl 19 had cryptorchism at birth At age 1 she had become physically retarded At 18 the left adrenal four times larger

[5] ... 1 28 29 6 7 1958

Tetrahydrocortisone and 11 ketopregnanetriol were identified but no 11β hydroxylated corticosteroids were detected Excretion of measurable amounts of tetrahydro S was found Complete absence of estriol was demonstrated

These findings support the conclusions of others that in congenital hyperplasia of the adrenals a number of different defects may arise in the enzymatic systems of the adrenal Greater attention should be given to the probability of transition from one pattern of steroid excretion to another

Congenital Adrenocortical Hyperplasia with Giant Cells in 12 Year Old Child is reported by M Loewenthal Hannah E Leszynsky M Marcus and H Zondek (Tel Aviv)

Girl 12½ who had been reared as a boy had advanced bodily development (Fig 59) but severe mental retardation Facial and body hair developed at age 6 The skin had shown a darkish brown tint since birth One brother was as darkly pigmented as the patient There was no pigmentation of the mucous membranes Somatic musculature was that of an adult man The hands and feet were small The voice was high pitched The phallus was 5 cm long and contained the opening of a blind duct The urethra opened near the phallic root No testes were present in the well developed scrotum or inguinal folds The blood pressure was 160 200/90 95 mm Hg Follicle stimulating hormone and luteinizing hormone excretion was less than 30 µl /L total estrogens were 500 µl /L 17 ketosteroids were 31 1 mg /24 hours and reducing corticosteroids after enzymatic hydrolysis were 10 2 mg /24 hours The blood concentration of the melanophore dispersing factor was 100 units/L (normal range up to 50 unit /L) The child died shortly afterward of bronchopneumonia Autopsy showed myocardial hypertrophy and mild myocarditis Minor cytologic changes in the pituitary consisted of slight increase in the chromophobe cells and slight reduction in the basophil cells The phallus was shown to be a clitoris The urethra opened into the vagina 8×3 cm in size A prostate was demonstrated at the junction of the urethra and vagina The uterus measured 5×2 5×1 5 cm and showed endometrial fibrosis and atrophy The ovaries were fibrotic and showed cystic degeneration A striking increase in the size of the adrenal (32 and 33 Gm) was caused by hyperplasia and also true cell hypertrophy with normal proportions present in the cortical layers Between the hypertrophic cells were many giantlike cells 100 µ in diameter embedded in cordlike groups which extended from the glomerular to the reticular zone and were prevalent in the fascicular zone Most of these cells had only one nucleus and the plasma nucleus ratio was normal a few had two or three nuclei There were no atypical mitoses but most of the giant cells were mere enlargements of the ordinary cortical element A few were genuine giant cells (Fig 60) with bizarre nuclei rich in chromatin which was coarse or granular

(5) J F doc 1 16 4 9 434 April 19 8

tion distinguished these from normal women Adrenal steroid hormones were elaborated in excess largely adrenal androgen Four women with hirsutism later proved to have Stein Leventhal syndrome were included because the sole criterion for inclusion was hirsutism Diagnosis was unequivocally established by direct examination of the ovaries These patients would have been classified as having hirsutism of undetermined cause if they had not later been subjected to laparotomy Adrenocortical hyperfunction was evident in each The adrenal cortex is probably involved in the clinical manifestations of this disorder

The principal alteration was elevated production of androsterone and etiocholanolone Each of the hirsute women produced abnormally large amounts of these two substances compared with normal women of commensurate age the amounts found equaled the production of these steroids by young normal men This is especially significant since besides the sex difference in adrenal function the male gonad contributes a portion of these metabolites

The evidence is substantial that in women as well as in men the adrenal cortex elaborates the principal precursors of the urinary metabolites studied Castrated men and women with intact adrenals continue to produce both androsterone and etiocholanolone but not if the adrenal is also removed Women and men markedly increase the production of these hormones when stimulated with corticotrophin and decrease production when given suppressive doses of cortisone These findings are explicable only if the adrenal cortex produces the precursors to the e substances In hirsute women cortisone or hydrocortisone administration results in a fall in production of androsterone and etiocholanolone to levels observed in normal nonhirsute women

The elevated levels of androsterone and etiocholanolone in hirsute women reflect adrenocortical hyperfunction Apparently the steroid metabolites isolated in abnormal amount are the same as those that result from metabolic transformation of known androgens The principal feature in these women are unmistakably androgenic Thus both clinical evidence and the chemical structure of the metabolites is compatible with the interpretation that the adrenal cortical secretion in these subjects is characterized by ex

than normal was removed It showed significant hyperpla ia of the cortex especially in the zona reticularis

The patient was reared as a boy a ociated with boys and had no libido Body build and hair pattern were male and the beard wa haved regularly The external genitalia showed a thumb ized phallus and igns of several surgical intervention for hypo padias Below the phallus was a scrotum like ma s which contained no teste X ray revealed a flat sella The blood level of protein bound iod ne was 3 4 μg /100 ml Urinary 17 ketosteroid excretion was 143 5 mg /day The dehydroandrosterone fraction was not increa ed

CASE 2 —Girl 23 sister of Ca e 1 had hown normal development as a child Around age 14 she began to shave She had had 2 opera tion for hypospadias She was reared as a boy as ociated with boys and had no sexual relation Body build wa male and a beard wa present She had a 3-cm phallus and a urethral opening under it Below it was a scrotum like mass without te te

X ray howed a normal ella Urinary 17 keto teroid excretion was 64 mg /day The dehydroepiandro terone fraction wa not in creased Perirenal air insufflation revealed enlargement of both adrenals

In both patients abdominal exploration revealed a smaller than normal uterus thin tubes and large gray white ovaries No testes were noted Uterus and adnexa were removed Histologic examination revealed hyperthecosis of the ovaries

Because of the patients resistance again t feminization cortisone treatment was abandoned in favor of ca tration It was believed that after ovariectomy the function of the adrenal cortex could be normalized with corti one or hydrocorti one without risk of feminization

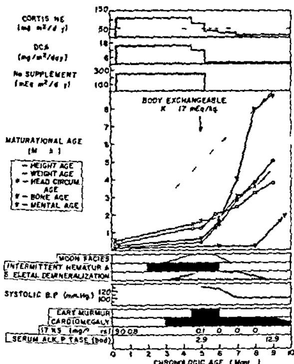
► [The occurrence of the ovarian changes characteri tic of the Stein Leventhal syndrome in women with Cu hing s di ea e and female p eudohermaphroditism has been known for many years This association i doubtless one of the features that led the authors of the following article to measure adrenal cortical function in hirsute women The tudies indi cate increa ed elaboration of androgens in the patients selected for study including 4 with the Stein Leventhal syndrome The generalization that all female hirsutism results from adrenogenital syndrome minor ha led to the administration of potent adrenal cortical steroid to far too many hairy girls It should be borne in mind that a modest degree of facial hir utism occurs in a very large percentage of normal fertile women —Ed]

Adrenocortical Hyperfunction in Idiopathic Hirsutism and Stein Leventhal Syndrome T F Gallagher Attallah Kappas Leon Hellman M B Lipsett O H Pear on and C D West (Sloan Kettering In t) studied 13 women un selected except for the presence of obviously exces ive hair growth A specific quantitative alteration in steroid produc

(7) J Cl n I t 37 94 99 J 19 8

tid upplement was discontinued Shortly thereafter the hea l cir cumt rence body length and weight began to incre e at a markedly accelerated rate (Fig 61) Motor and intellectual achievement re sponded rapidly

U e of the rate of statural growth and occa ional ob erva



F g 61 —Effect f te d dosage on l al ou se d labo atory find ng D nal b ken l e p esent po t t wh h matu at on l ge w ll f ll n rmal male ch ld (Courtesy of D esch N N l T lbot N B N w E gl nd J Med 2 7 1 8 1 3 Dec 6 1957)

tions of skeletal maturation as guides to cortisone dosage in infants and children may avert such difficulties

► (This is a timely warning While the results of corticoid therapy of congenital virilizing adrenal cortical hyperplasia have been revolutionary it must be remembered that overdoses of corticoids produce many harmful effects including stunting of growth. From a historical standpoint the fir t evidence of the metabolic actions of corticotrophin was inhibition of somatic growth in castrate rat (Moon H D Proc Soc Exper Biol & Med 37 34 1937) This was an amazing observation at the time since all previou pituitary extracts had stimulated growth. Nitrogen-excreting ac tivity of corticotrophin w s shown sub equently in the normal rat (Gordan

cessive production of adrenal androgen Some of the women showed elevated production of C_{19} 11 oxygenated steroids Thus the increased adrenal function was not limited to metabolites of 11 desoxysteroid hormones but these showed the greatest elevation

The demonstrated adrenocortical hyperactivity in the 4 women with Stein Leventhal syndrome was particularly interesting Previous studies of neutral 17 ketosteroids had been nonrevealing More detailed steroid analyses will probably reveal significant hormone alterations in a number of these women In fact altered adrenal function may be a significant or even primary influence in this disorder

Hirsute women in this study demonstrated increased production of androsterone and etiocholanolone unaccompanied by increased secretion of hydrocortisone or chemically related hormones These women did not exhibit signs and symptoms of Cushing s syndrome The biochemical lesion is an adrenal hyperfunction largely limited to the adrenal androgen

Developmental Arrest Due to Corticosteroid Intoxication in Infant with Adrenocortical Virilism was observed by *Alexander N Drescher and Nathan B Talbot*[8] (Harvard Med School)

Boy was born with adrenocortical virilism with a sodium losing component Treatment was begun with cortisone *110 mg /sq m body* surface/day desoxycorticosterone acetate (DCA) 16 mg /sq m / day and sodium chloride 250 mEq /sq m /day He improved and was sent *home on this regimen which was followed until* age 4½ months when cortisone was reduced to 80 mg and DCA to 12 5 mg / sq m At age 5 months he had the proportions and behavior pat*terns of a newborn Height* was *comparable* with *that of* a 6 week old boy weight with that of a 4 week old boy and head circumference was at the 0th percentile for newborns There were marked weak*ness moderate hypotonia* and inability to maintain head position Systolic blood pressure was 130 mm Hg The heart was enlarged with a loud systolic murmur Serum electrolytes were normal but serum alkaline phosphatase was only 2 9 Bodansky units/100 ml Intermittent hematuria was present X ray films showed generalized demineralization in the skeleton and bone age corresponded to that of a newborn The body exchangeable potassium was markedly reduced the sodium normal With this evidence of excessive *steroid* therapy cortisone was decreased to 40 mg /sq m /day and DCA to about 1 5 mg /sq m /day (in a 75 mg pellet) and the sodium chlo

(8) New Engl J Med 257 1280 1 8 Dec 6 1957

ride supplement was discontinued Shortly thereafter the head circumference body length and weight began to increase at a markedly accelerated rate (Fig 61) Motor and intellectual achievements responded rapidly

Use of the rate of statural growth and occasional observa

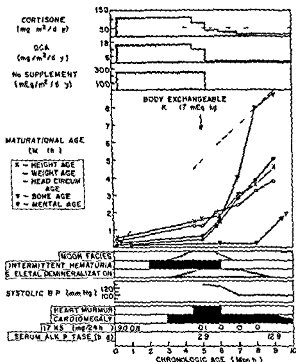


Fig 61—Eff t of t d d ge n l l) labo t y fi) g D k t b k l p t po t at wh h m t t) w ll f ll g m l m l ch ld (C t r f D sch A N (Tall t N B N w E gl d J M d 257 1280 128 D 26 195)

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G S Li C H and Bennett L L ibid 262 103 1946) and shortly thereafter in man by Sprague and his co workers at the Mayo Clin (Arch Int Med 85 199 1950) —Ed]

Experience with Use of 6 Methylprednisolone in Adrenogenital Syndrome The adrenogenital syndrome caused by congenital adrenal cortical hyperplasia is attributable to an inborn error of metabolism Hydrocortisone cannot be synthesized and a number of abnormal urinary steroid metabolites are found in large amounts as a consequence of persistent adrenocorticotrophic stimulation The increased excretion of 17 ketosteroids can be suppressed by administering hydrocortisone cortisone or other glucocorticoids The large quantities of pregnanetriol in the urine are due to an abnormal accumulation of 17 hydroxyprogesterone an intermediate in the adrenal synthesis of hydrocortisone Thus in patients with this disorder the effects of various analogues of hydrocortisone on the secretion of adrenocorticotrophic hormone can be observed by the alterations in urinary 17 ketosteroids and pregnanetriol

Alfred Bongiovanni and Walter R Eberlein[9] (Univ of Pennsylvania) administered Medrol® (6 methylprednisolone) orally to 5 patients with this syndrome Three had the uncomplicated form 2 the hypertensive form Medrol® successfully maintained suppression of abnormal urinary steroid metabolites in doses about one fifth to one seventh those of hydrocortisone In 1 patient control of hypertension and edema was better than with hydrocortisone In all other respects Medrol® fulfilled the requirements for adequate control of the disease No detrimental effects were observed

Pregnancy Following Treatment of Congenital Adrenal Hyperplasia with Cortisone terminated successfully with the birth of normal living infants in 2 case reports by Robert B Wilson and F Raymond Keating Jr[1] (Mayo Clinic and Found)

Woman 22 had amenorrhea marked masculinization and hirsutism (Fig 62) The clitoris was 4 5 cm in length the vagina deep and narrow and the uterus and cervix were very small Excretion of estrogens was 53 rat unit /24 hours and urinary pituitary gonadotrophin was zero Excretion of 17 ketosteroids was 86 mg /24 hour Classic female pseudohermaphroditism associated with congenital ad

(9) Metabolism 7 (pt) 457 46 July 19 8
(1) Am J Obst & Gynec 6 388 397 August 1958

Treatment with adrenal steroids was started. Menses began 2 months later and occurred at 26 day intervals until she became pregnant the renocortical hyperplasia was diagnosed. Laparotomy was declined by the patient. Nine years later she returned with no significant change in physical findings and with persistence of amenorrhea

A B

[illegible] & Gyn 76 358 [illegible] 19 8 [illegible]

following year. The prenatal course [illegible] uneventful. Steroids were given in varying amounts [illegible] of prednisone was 5 mg every 12 hours during the 31 [illegible] pregnancy. Delivery by cesarean section was necessitated [illegible] of a contracted pelvis. Cortisone was given before and after delivery. The baby weighed [illegible] Gm and was entirely normal. The patient discontinued cortisone therapy when she left the hospital. No withdrawal symptoms were noted. Follow up has not been satisfactory.

This patient and the other one reported on by the authors had anatomically normal female genitourinary tracts and both were reared as females Therapeutically they po ed no particular problem once adrenal suppression had been effected with cortisone Periodic assay of urinary 17 ketosteroids is required in management of patients with adrenogenital syndrome Protecting the patient with large quantities of corti one before delivery or other stress should be emphasized inasmuch as it is improbable that they can be adequately protected by their own adrenal cortices Corti one 200 mg is given intramuscularly 2 3 times within the 36 hours preceding the stressful situation blood pressure levels and parenteral fluid therapy are closely watched ub e quently and further replacement therapy is dictated by the patient s course

The delivery of normal female infants in these 2 cases indicates that the levels of androgen secretion were insufficient to produce harmful effects on the genitourinary development of the babies

► [As far as I know this is the first reported successful pregnancy in a female pseudohermaphrodite who e endocrine defect was corrected by the administration of cortisone In the only case reported before Bartter s introduction of cortisone for the treatment of this condition that of Cotte (J Mt Sinai Hospital New York 14 170 1957) the criteria for the diagnosis of adrenal cortical hyperplasia were not complete —Ed]

NEOPLASTIC ADRENOGENITAL SYNDROMES

► As can be seen from the previous and subsequent paper the term adrenogenital syndrome is used indiscriminately to indicate many divergent states of adrenal hyperplasia or tumor resulting in different clinical manifestations depending on the age and sex of the host and the ratio of estrogens androgen and corticoids secreted Because of its non pecificity I would like to nominate this term for oblivion —Ed

Unusual Findings in Case of Adrenogenital Syndrome Due to Adrenal Tumor are reported by Bernhard Zondek Daniel Diengott and Michael Finkel tein* (Hebrew Univ Jerusalem)

Woman 58 had pronounced virilization including hir uti m over the face and body loss of scalp hair and a deep male voice as well as constantly increasing headaches and increasing blood pre sure up to 220/100 mm. but urinary excretion of 17 ketosteroids was not significantly increased Administration of cortisone cau ed a remarkable rise in excretion of the 17 keto teroids from about 14

( ) A ta med e t 16 266-268 Nov Dec 1957

mg /24 hours in the pretreatment period to about 60 mg /24 hours for 10 days after discontinuation of cortisone medication Excretion of estrogens estimated by bioassay and fluorometry was considerably increased over normal The neutral fluorogenic fraction was increased as occurs in female pseudohermaphroditism due to adrenal hyperplasia The fluorogenic material was definitely not pregnanetriolone Pregnane 3α 17α 20α triol 11-one excretion of which is considered specific to virilizing adrenal hyperplasia was not found in the urine Hence the presence of a tumor was considered and found at operation

Postoperative complications which included bone decalcification failure in healing of an arm fracture and mental disturbances readily responded to therapy with *stilbestrol* (This therapy was given because in experiments on rats and cocks stilbestrol caused calcemia and bone formation) Several weeks after the *operation* the severe headache disappeared and blood pressure returned to normal After several months baldness completely disappeared beard growth decreased feminine characteristics increased and the patient s external appearance became nearly that of a normal woman her age

Case of Feminizing Adrenal Tumor in Girl A *H* Smith[3] (Hosp for Sick Children London) presents a case

Girl 5½ had breast enlargement pubic hair and vaginal bleeding since age 4 Blood pressure was 110/80 mild acne was present the vulva was adult in appearance but the clitoris was not disproportionately enlarged Bone age was about 12 years The polymorphonuclear leukocyte chromosomal pattern was typically that of the female The vaginal smear showed complete estrogenization Presacral gas insufflation showed an enlarged right adrenal gland Right adrenalectomy revealed an adrenocortical neoplasm with anaplastic changes but no definite evidence of malignancy Within a month after removal of the tumor breasts became smaller and 4 months later pubic and axillary hair as well as breast development regressed The vulva was unchanged

The 17 ketosteroid excretion before surgery was 17 5 and 20 7 mg /24 hours and after surgery 2 5 and 1 95 mg The 17 hydroxysteroids were 3 2 and 6 7 mg /24 hours before operation and 6 and 6 1 mg afterward Estrone excretion was 10 3 and 12 1 μg /24 hours preoperatively and fell to 0 and 0 8 μg 17β e tradiol was 5 1 3 8 and 3 4 μg /24 hours before operation and disappeared entirely and estriol was 16 4 4 and 5 1 μg 24 hours before and less than 1 and 0 8 μg after operation Total estrogens were 31 4 18 5 and 20 6 μg 24 hours before and less than 1 and 1 6 μg after operation

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(3) J Cl E 1 3 28 318 3 31 h 1958

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( ) A ta m d ent 16 266 268 N v D 1957

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( ) Acta med o ent 16 266 68 N v De 1957

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Postoperative complications, which included bone decalcification, failure in healing of an arm fracture and mental disturbances, readily responded to therapy with stilbestrol. (This therapy was given because in experiments on rats and cocks stilbestrol caused calcemia and bone formation.) Several weeks after the operation the severe headache disappeared and blood pressure returned to normal. After several months baldness completely disappeared, beard growth decreased, feminine characteristics increased and the patient's external appearance became nearly that of a normal woman her age.

Case of Feminizing Adrenal Tumor in Girl.—A. H. Snaith[3] (Hosp. for Sick Children, London) presents a case.

Girl, 5½, had breast enlargement, pubic hair and vaginal bleeding since age 4. Blood pressure was 110/80, mild acne was present, the vulva was adult in appearance, but the clitoris was not disproportionately enlarged. Bone age was about 12 years. The polymorphonuclear leukocyte chromosomal pattern was typically that of the female. The vaginal smear showed complete estrogenization. Presacral gas insufflation showed an enlarged right adrenal gland. Right adrenalectomy revealed an adrenocortical neoplasm with anaplastic changes but no definite evidence of malignancy. Within a month after removal of the tumor breasts became smaller and 4 months later pubic and axillary hair as well as breast development regressed. The vulva was unchanged.

The 17-ketosteroid excretion before surgery was 17.5 and 20.7 mg./24 hours and after surgery 2.5 and 1.95 mg. The 17-hydroxysteroids were 3.2 and 6.7 mg./24 hours before operation and 6 and 6.1 mg. afterward. Estrone excretion was 10.3 and 12.1 μg./24 hours preoperatively and fell to 0 and 0.8 μg. 17β-estradiol was 5.1, 3.8 and 3.4 μg./24 hours before operation and disappeared entirely, and estriol was 16, 4.4 and 5.1 μg./24 hours before and less than 1 and 0.8 μg. after operation. Total estrogens were 31.4, 18.5 and 20.6 μg./24 hours before and less than 1 and 1.6 μg. after operation.

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(3) J. Clin. Endocrinol. 18:318, March, 1958.

berty the level of 17 ketosteroid excretion suggested an adrenal tumor Estrogen excretion was as high as in precocious puberty but was probably elevated because of the adrenal tumor Of particular importance was the absence of signs of Cushing s syndrome and of abnormal virilism

Adrenocortical Carcinoma Causing Feminization in Adult Male Hormonal Considerations and Results of Heterotransplantation of Tumor in Guinea Pigs E Trowbridge Wolf Lewis C Mills Berne L Newton L L D Tuttle Robert A Hetti_g Vincent P Collins and William B Gordon[4] (Baylor Univ) describe a man 46 who had an adrenocortical carcinoma with gynecomastia loss of libido recent appearance of a left sided varicocele and increased urinary excretion of estrogens Urinary 17 ketosteroid 17 hydroxycorticoids and pregnanediol were also increased After the tumor was removed libido returned to normal and gynecomastia subsided Urinary steroid excretion *fell to within* normal limits except for pregnanediol which remained elevated but was considerably below preoperative level

The adrenal tumor of this patient was successfully transplanted into the anterior chamber of a guinea pig eye The transplants maintained their ability to secrete estrogens and regressed after x irradiation

► [The term feminization as used indicates gynecomastia and loss of libido It will be noted that urinary estrogen were not the only hormonal metabolites that were increased but also 17 ketosteroids corticoid and pregnanediol Since the adrenal normally makes androgens and androgens are normally metabolized to estrogens and since administration of androgens frequently leads to gynecomastia the term feminization may be somewhat misleading We described a similar case as one of Adrenal Cortical Carcinoma with Excess Androgen Production in an Adult Man (Kerr W J and Gordan G S Postgrad Med 11 276 1952) The similar observation of gynecomastia in association *with interstitial cell tumor* of the testes has been reported from Paris and from New Haven (see section on The Reproductive System) —Ed]

OTHER ADRENAL CORTICAL TUMORS

Adrenal Cortical Carcinoma Associated with Hypoglycemia is reported by C L Aszkanazy L Jenkins and W W Simpson (Univ of British Columbia) Not only was insulin absent from the main tumor and its metastases but the pan

(4) J Clin Endocr 18 310 31 M h 19 8
(5) Ca d M A J 79 48 -484 Sept 15 1958

creas also had only a normal insulin content so that the fortuitous presence of a small functioning islet cell adenoma could be excluded

Woman 26 had a history of low blood sugar attacks of low back pain enlargement of the abdomen and episodes of epigastric discomfort She was admitted to the hospital in coma She was pale and had a cool moist skin The pulse rate was 110 blood pressure 130/70 and respirations 18 Reflexes were hyperactive and there was prolonged ankle clonus but the plantar responses were absent The extremities were rigid and extended with a bilateral carpopedal spasm A large mass was palpable in the left upper quadrant of the abdomen extending to 4 cm below the left costal margin Blood sugar was 37 mg/100 ml Otherwise urine blood and cerebrospinal fluid were normal An ECG showed sinus tachycardia at 110/minute an EEG was diffusely abnormal from a deep midline origin (blood sugar level at that time was 96 mg/100 ml) A barium meal revealed an extrinsic retroperitoneal mass An intravenous pyelogram was normal but the left kidney was depressed and rotated A large tumor was found at the upper pole of the left kidney and metastases were noted in the liver The pancreas lay in front of the tumor but appeared normal Biopsy specimens from the main mass and a liver metastasis showed anaplastic carcinoma The patient died about 1 month after hospitalization during an episode in which no blood sugar was demonstrable

To date no satisfactory explanation exists for the hypoglycemia associated with nonpancreatic tumors The most plausible hypothesis is that these tumors by virtue of their location and large size stretch the sympathetic nerve trunks or receptors in the liver adrenals and pancreas and thus interfere with glycogen mobilization

► [This is one of the rarest clinical syndromes associated with adrenal cortical tumor and the pathogenesis is a complete mystery The only similar cases which come to mind are those of Staffieri (J Clin Endocrinol 9 255 1949) and Anderson (Am J M Sc 180 71 1930) —Ed]

Studies of Adrenal Cortical Function in Three Cases of Carcinoma are reported in detail by Charles H Lockwood[6] (London Ont) and illustrate the variable clinical manifestations of adrenal cortical hyperfunction

Case 1 —Woman 53 with classic Cushing s syndrome associated with widespread metastases from a breast carcinoma showed masculinization and elevated urinary 17 ketosteroid excretion Mineralocorticoid (aldosterone) effect was present intermittently throughout her illness and hypokalemia was reported on several occasions Autopsy revealed marked cortical hyperplasia of the adrenal but no demonstrable tumor The infiltrating ductal carcinoma of the breast

(6) Canad M A J 79 835 Nov 1 1958

had metastasized to the left lung, pleura and liver. Acute interstitial pancreatitis was also present. Despite 2 courses of irradiation the pituitary showed only degeneration of basophilic cells regarded as secondary to adrenal cortical hyperplasia.

CASE 2.—Man, 61, with primary oat cell carcinoma of the lung metastatic to mediastinal lymph nodes and liver, had no physical features of Cushing's syndrome. Hypertension and hypokalemia suggested hyperaldosteronism. There was increased glucocorticoid, aldosterone and ketosteroid excretion, but there was no physical evidence of the glucocorticoid or the androgen excess. Severe metabolic imbalance was present and bilateral adrenalectomy was performed to attempt to stabilize the patient's condition. Adrenal glands showed cortical hyperplasia and metastatic carcinoma.

CASE 3.—Man, 70, was operated on for a large abdominal mass which had not appeared to be a functioning endocrine tumor. The tumor was shown to be an adrenal cortical carcinoma producing mainly androgenic hormones with an elevated 17-ketosteroid excretion. The total urinary glucocorticoids were elevated after corticotrophin therapy postoperatively, the increase being small in comparison with the marked elevation of urinary 17-ketosteroids after such therapy.

The association of adrenal cortical hyperplasia and hyperfunction with carcinomatosis in Cases 1 and 2 is unusual. Case 1 had the classic physical features of Cushing's syndrome, whereas in Case 2 laboratory findings were in keeping with Cushing's syndrome but physical features of the syndrome were absent. Cushing's syndrome has been described in association with carcinoma of the bronchus, pancreas and thymus, diseases of the liver and tumors of the ovaries. Case 3 is presented for contrast: despite the large mass of malignant adrenal cortical cells, there was no clinical suspicion that the tumor was producing an increased amount of hormone.

Does Adrenocortical Hyperplasia Result in Adrenocortical Carcinoma? Such a possibility may have support in a patient reported on by *George J. Hamwi, Richard A. Serbin* and *Fred A. Kruger* (Ohio State Univ.) in whom symptoms of masculinization were present for 30 years before excision of an adrenocortical carcinoma. There was responsiveness to stimulation by corticotrophin and to inhibition by adrenal corticoids.

Woman, 37, with chest hair, deepening of voice and a beard requiring daily shaving for 30 years, showed 17-ketosteroid excretion

( ) New England J. Med. 257:1153-1157, Dec. 12, 1957.

ranging from 80 to 185 mg /24 hours She had had clitoridal hyper trophy followed by clitoridectomy At age 17 17 ketosteroid excre tion had been as high as 83 2 mg /24 hours Hypoplastic internal genitalia had been noted

After administration of 9α fluorocortisol excretion of 17 keto te roid decreased to 40-50 mg /24 hours After 25 mg corticotrophin intravenously 17 keto teroid excretion exceeded 200 mg /24 hours Plasma level of 17 hydroxycorticoids (7 7.7 μg /100 ml) failed to increase under corticotrophin stimulation Pregnanetriol levels in the urine were consistently elevated ranging from 11 to 60 mg /24 hours Dehydroepiandrosterone was absent from the urine However x rays demonstrated a tumor in the region of the upper pole of the left kidney A multilobular tumor weighing 228 Gm proved to be a well differentiated adrenocortical carcinoma invading fat and lymph nodes Postoperative cour e was uneventful and the patient was maintained on suppressive therapy with 5 mg prednisone 3 times daily

The possibility that prolonged stimulation by corticotro phin resulted in hyperplasia of the adrenal gland and that the hyperplastic tissue later became a malignant tumor must be considered This is the most reasonable explanation of the chemical findings and the clinical course as pre ented even though no direct proof can be offered An alternative e planation—that this had been a carcinoma from inception—would postulate extremely slow tumor growth

► [When S L Simp on suggested a similar hypothesis some 10 years ago it struck me as unlikely since I knew of no such instance in the very large number of reported cases of congenital virilizing hyperplasias or in Cush ing s disease —Ed]

THE REPRODUCTIVE SYSTEM

► Disorder of sex differentiation are now beginn ng t fi int> logical sequence as a esult of sexing by means of chr matı ı patter ı The difficult feat of d agnosing gonadal dysgenesis in prepuberal cl ldren first accom plished by Grilberg (J Clin Endocrinol 7 11 134) but o rarely achieved by others that many authorities have onsidered it impo sible has now been made feasible in many children even unborn As might be anticipate I the a ociat on of gon dal dysgenesis with anomalies of the kid ney which also ar es from the urogenital ridge is now being describe I Seminife m tul uar dysgenesis once a rare d ease is now recog ize l with remarkable frequency Studies are under vay to e tablish whether the t o conditior gonadal dysgenesis and eminif rous tubular dy s, ne are ruly almost complete sex reversals Studies are also under wa to de term ne whether the chromatin blob of the latter represents an XXY rath r than an XX chromosome and the chromo omes of the form r have an XO rath r than an XY configuration Kno vledge of the nature of gonadotro

phins in man and the factors controlling their secretion i only now as um ing definitive proportions Further evidence ha been obtained that elabora tion and release of these important hormones are controlled both from above and below i e from suprasellar center in the brain and by gonadal secretions Likewise knowledge of the nature of the hormones elaborated by the ovary has been extended by Zander s demon tration that the corpu luteum and placenta form both the 20α and 20β alcohol of 3 ketopreg n-4 ene Chemically these compound may be looked on a degradation products of progesterone but since both have proge tational activity they must be added to the li t of natural progestational agent Many synthetic compound with similar activity have been de cribed particularly in the 19 norte tosterone erie These combine progestati nal anabolic, androgenic estrogenic and ovulation inhibiting capacity Of cour e progesterone and anhydrohydroxyprogesterone (ethynyl testo terone) al o are weak androgen a point which has acquired new clinical significance becau e of occasional ma culinization of female fetuses born of mother who have been treated with the e agent Since estrogen and androgen alter blood lipid patterns in opposite direction we all have been curiou to ee what effect compound with both activities would have on lipids These actions have been reported within the past few years It i al o of interest to know that the beta lipoprotein elevating effect of methylte to terone can be abol ished by limiting the patient s intake of protein Of particular significance is the report of Hertz Bergenstal and co-workers that methotrexate turns off hormonal secretion of choriocarcinomas of women and al o produce regres ion of the tumors presumably by interfering with their folic acid metaboli m The use of fluoxyme terone and other androgens in the treat ment of carcinoma of the breast is described in the ection on Endocrine Influences on Neoplastic Di ea es A report of Cu hing s yndrome even tuating from carcinoma of the ovary is included in the ection on The Adre nal Cortex Included in the section on Carbohydrate Metaboli m are re ports on pregnancy complicated by diabetes mellitus and of the curiou ability of 17α ethyl 19 norte tosterone to abolish the hyperglycemic action of glucagon

The rapid development in embryology endocrinology and cytology which have completely revolutionized our knowledge of sex differentiation require pecialized information for an accurate interpretation and applica tion to clinical disorders I am therefore particularl grateful to Dr Mel vin Grumbach for the following pecial article which bring u up to date on the many recent advances in this field—Ed

Spec al Art cle

THE SEX CHROMATIN PATTERN AND HUMAN SEXUAL ANOMALIES

by Mel M Grumba h M D

A continuing impetus to investigations in the field of hu man intersexuality has been provided by Barr s di covery of a relatively simple method for asses ing chromosomal sex The detection of what i now known as nuclear sex as well as recent developments in cytogenetics embryology and biochemistry have profoundly altered concepts of sexual anomalies in man Within the past 4 years three previou ly unrecognized forms of intersexuality have been defined gonadal dysgenesis in chromo omal males phenotypic males with testes and chromatin po itive (female) nuclei and phenotypic female with ovaries and chromatin negative (male) nuclei

Our knowledge along these lines is expanding at an ac celerated pace but at the moment a full measure of pru dence garnished with judicious skepticism is to be recom mended in some areas Current thought on certain as pects e pecially those concerning etiology should not be accepted as more than hypothesis until more fact become available This review will discuss briefly e impl ation of new de elopments in anomalies of ex

CYTOLOGIC TESTS OF CHROMO OMAL SEX

It is now w ll established that the ex chromatin as seen in somatic cell is a distinguishing mark of chromosomal sex However in ap lying this technic in patients with abnor malities of ex lifferentiation the pos ibility of an unu ual sex c romo ome complement such as XXY or XO should be born in mind A substantial body of indirect eviden in dicates that chromatin positive (female) nuclei c ntain a pair of XX chr mo omes but doe not exclude the pre ence

D partm t f P d t Colleg f Ph d S geo C l mb U
ty d B H p t l N w Y k

in certain intersexes of an additional sex chromosome Similarly in chromatin negative cases one cannot on the basis of a cytologic test rule out for example an XO sex chromosome constitution The recent application of cytogenetic technics to investigations along these lines should resolve by direct examination of the chromosomes the question of chromosomal aberrations

There is evidence that in blood films obtained from females the drumstick shaped nodule of chromatin on the nuclei of some polymorphs described by Davidson and Smith does not correlate perfectly with the sex chromatin mass found in the nuclei of other somatic cells of the same persons In some forms of intersexuality the discrepancies between neutrophil sex and nuclear sex as determined by the oral smear or skin biopsy method suggest that polymorph structure is not always a valid indication of the sex chromatin pattern in other tissues For the present it ought not be relied on for routine diagnosis

It is now well accepted that the sex of the zygote at fertilization is established by a chromosomal mechanism which results in an unequal balance of sex determining genes Further it seems probable that the sex determining genes direct the differentiation and development of the gonad through their action on specific chemical processes In accordance with genetic sex an orderly sequence of changes brings about the transformation of a sexually bipotential organism into either a male or female fetus These changes involve successively the gonads the genital ducts and finally the urogenital sinus and external genitalia

The bipotential gonad is composed of two somatic unipotential primordia—a cortical element which can develop only as an ovary and a medullary element capable of differentiating as a testis The bipotential germ cells which arise elsewhere constitute the germinal component It is postulated that the cortex and medulla induce development of the primordial germ cells as either oogonia or spermatogonia Witschi has recently reaffirmed on the basis of nuclear sex determinations in human embryos the identical early morphologic characteristics of the primitive gonad later destined to develop as either a testis or an ovary

The concept of corticomedullary interaction or balance

with its mutually antagonistic physiologic relationship between the cortex and the medulla has been well established in lower animals and is discussed in detail elsewhere This concept has important implications as to the mechanism of reversal or inversion of gonadal development in man It affords an explanation of the occurrence of chromatin positive persons with testes which may contain spermatozoa of chromatin negative persons with ovaries containing ovocytes and of either chromatin negative or chromatin positive persons with both ovarian and testicular tissue Although the competitive relationship between cortex and medulla is gene controlled and the outcome normally is determined by genetic sex a variety of experimental procedures can alter the balance between the cortex and medulla contrary to genetic sex through inhibition of the dominant element There is good evidence supported recently by in vivo studies in tissue culture that gonadal differentiation in placental mammals is effected through a humoral sex differentiating substance the nature of these embryonic sex inductors or sex hormones—a lively subject of controversy in embryologic circles—is unknown

Somatic sex differentiation a term which refers to the development of the genital ducts and lower genital tract is mainly a hormonal process It has been shown by Jost and others in placental mammals that the fetal testis and its morphogenetic hormone play a major role Absence of the testis at a critical stage results in entirely female differentiation of the accessory sex structures Partial fetal testicular insufficiency during the crucial phase of embryonic sex differentiation can lead to varying degrees of ambisexual development e g from males with hypospadias to male with female external genitalia Variations in time of onset degree duration and laterality of the deficiency of the testicular morphogenetic hormone would largely determine the extent and type of abnormal differentiation of the genital ducts and of the urogenital sinus and external genitalia

Whereas a functioning fetal gonad is not a prerequisite for the development of a female genital system exposure of the female fetus to androgenic hormones can arrest female differentiation of the urogenital sinus and external genitalia and induce masculinization of the lower genital tract

It also should be emphasized that apart from disturbances in the hormonal milieu of the fetus malformations of the genital system can arise from other factors which may have a deleterious effect on the preprimordia of the genital structures or the primordia themselve Not infrequently anomalies of this type are associated with defective development of the urinary tract and the cloaca

Abnormalities of Sex Differentiation

Knowledge of the embryologic basis for human sexual anomalie is necessary for an understanding of the morphologic variations which are encountered clinically in human inter exes Because of our lack of knowledge or uncertainty of etiologic factors in most instances at the present time classification of intersexes is largely ba ed on morphologic and pathogenetic considerations

A revision of the nomenclature of intersexuality is needed However until there is general agreement on a new terminology it seems wise to adhere as closely as possible to that in current use despite its obvious limitation

There also remains much to be learned about the nosology of intersexes As more knowledge of etiologic factors i obtained a more comprehensive classification should be possible In the following discussion the classification proposed by Grumbach and Barr (Recent Prog Hormone Re 14 2 1958) will be used One point concerning present system of classification de erves particular emphasis Terms such as female pseudohermaphroditism and male p eudohermaphroditism describe a group of disorders which share in common certain morphologic characteristics As in congestive heart failure the causal factors and the specific disorder which produce the e syndromes may be diver e

Female Pseudohermaphroditism

The above concept is well illustrated by female pseudohermaphroditism a syndrome in which knowledge of etiologic factor is more advanced than in many other forms of in a intersexuality The syndrome serve to emphasize the complexity of pathogenetic factors which may result in similar malformations Table 1 contains a cla sification of

female pseudohermaphroditism divided according to etiology into two groups forms in which the syndrome is androgen induced and forms in which it is due to other teratogenic factors

By far the commonest cause is congenital virilizing adrenal hyperplasia The minimum incidence of the disorder has been estimated at 1 in 67 000 births This inborn error in the hydroxylation of C_{21} steroids by the adrenal cortex is inherited as a recessive trait and is in itself a heterogeneous disorder Three forms of the disease have been described each of which in the female may be associated with female pseudohermaphroditism The masculinization of the external genitalia is a consequence of excessive secretion of androgens by the abnormal fetal adrenal Present evidence would suggest that the three well defined clinical variants involve three different mutant genes and enzymatic defects

TABLE 1—CLASSIFICATION OF FEMALE PSEUDOHERMAPHRODITISM

A ANDROGEN INDUCED
Fetal source
1 Congenital virilizing adrenal hyperplasia
a Virilism only (defective adrenal 21 hydroxylation)
b Virilism with hypertension (defective adrenal 11 hydroxylation)
c Virilism with salt losing syndrome (defective adrenal 21 hydroxylation + ?)
Maternal source
1 Virilizing ovarian tumor
2 Iatrogenic
a Testosterone and related steroid
b Synthetic progestational steroids and proge [illegible]
B OTHER TERATOGENIC FACTORS
Nonh[illegible]al disturbances in the differ[illegible] [illegible] structure

A le[illegible] common type of androgen induced female pseudohermaphroditism is caused by transmission of androgens by the mother during pregnancy In two instances a virilizing ovarian tumor in the mother during pregnancy has been associated with partial masculinization of the external genitalia of the female fetus Varying degrees of fetal masculinization have been observed in the female offspring of mothers who were given various testosterone or testosterone like preparations during pregnancy Wilkins *et al* (J Clin Endocrinol 18 559 1958) have recently reported 17 cases associated with the administration of 17 ethinyltestosterone

It al o should be emphasized that apart from disturbances in the hormonal milieu of the fetus malformations of the genital system can arise from other factors which may have a deleterious effect on the preprimordia of the genital structures or the primordia themselves Not infrequently anomalie of this type are as ociated with defective development of the urinary tract and the cloaca

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ment of breasts and a female habitus at puberty Essentially these are amenorrheal women with testes and a male chromosomal pattern of somatic cells The vagina consists of a blind pouch and commonly there is predominantly masculine differentiation of the genital ducts In a variant of this syndrome more masculine differentiation of the external genitalia is found The defective testes which in some cases contain spermatogenic elements *may be situated intra*abdominally or in inguinal or labial herniae The testes show a propensity to undergo malignant degeneration Castration is followed by a fall in urinary estrogens a rise in gonadotrophins and often the onset of menopausal symptoms

The high familial incidence of both the complete and par

TABLE 2—CLASSIFICATION OF MALE PSEUDOHERMAPHRODITISM

1. Variant of gonadal dysgenesis in chromosomal males
2. *Syndrome of feminizing testes*
   a. Complete—*female* external genitalia
   b. Incomplete—ambiguous external genitalia
3. With female ducts and male external genitalia
4. With nonvirilizing adrenal hyperplasia adrenal insufficiency and female external genitalia
5. Other forms

tial forms of the syndrome of feminizing testes suggests a genetically determined disorder An analysis by Grumbach and Barr of 16 pedigrees by the proband method showed a familial aggregation of affected cases consistent with either a sex linked or a sex limited dominant trait The action of the mutant gene is not known but it clearly results in partial fetal testicular insufficiency and perhaps in some enzymatic defect in the synthesis of testicular hormones In addition Wilkins has obtained suggestive evidence of end organ insensitivity to androgen

Witschi Nelson and Segal have advanced the hypothesis that the mothers of affected males transmit an antitestis substance during pregnancy—possibly an antibody

Syndrome of Gonadal Dysgenesis

The typical form of this syndrome with its cardinal features of a female phenotype rudimentary gonads sexual infantilism short stature and associated anomalies is well recognized About 80 % of subjects with gonadal dysgenesis have male [illegible]

orally or progesterone parenterally to pregnant women In addition we have recently observed 5 cases in which the mother had received one of the new synthetic oral progestational steroids—Norlutin (17α ethynyl 19 nortestosterone) or Enovid (norethynodrel) Virilization did not progress after birth in any of these cases

There is a third distinct group of female pseudohermaphrodites of quite different etiology In these case the teratogenic factor seems unrelated to the direct action on the female fetus of excessive amounts of androgens instead development of the primordia is in itself defective Associated developmental anomalies of the urinary tract and the cloaca as well as absence of the genital duct (most often unilateral) or the ovary are not uncommon

Hence in female pseudohermaphroditism the abnormal sex differentiation may be a consequence of an abnormal hormonal environment of the female fetus due to the action of a single mutant gene or to an exogenous hormone transmitted by the mother Contrariwise in rare cases the anomalous development may be a consequence of an unknown teratogenic factor resulting in regional disturbances in the morphogenesis of the genital primordia unrelated to an androgenic agent

In one variant of this group with unilateral or bilateral renal agenesis there are striking similarities to the genetically determined malformations of the genitourinary system described in rats of the AxC strain and in mice

Male Pseudohermaphroditism

Male pseudohermaphroditism is another syndrome which occurs in a heterogeneous group of disorders This group includes chromosomal males with testes and ambisexual differentiation of either or both genital ducts and the urogenital sinus and external genitalia There are four distinct categories to which many but not all of these patients can be assigned (Table 2)

A frequent if not the most common form of male pseudohermaphroditism is the syndrome of feminizing testes The complete form of this syndrome is characterized by female external genitalia primary amenorrhea absent or scanty pubic and axillary hair in most cases and develop

ment of breasts and a female habitus at puberty Essentially these are amenorrheal women with testes and a male chromosomal pattern of somatic cells The vagina consists of a blind pouch and commonly there is predominantly masculine differentiation of the genital ducts In a variant of this syndrome more masculine differentiation of the external genitalia is found The defective testes which in some cases contain spermatogenic elements may be situated intra abdominally or in inguinal or labial herniae The testes show a propensity to undergo malignant degeneration Castration is followed by a fall in urinary estrogens a rise in gonadotrophins and often the onset of menopausal symptoms

The high familial incidence of both the complete and par

TABLE 2—CLASSIFICATION OF MALE PSEUDOHERMAPHRODITISM

1 Variant of gonadal dysgenesis in chromosomal males
2 Syndrome of feminizing testes
   a Complete—female external genitalia
   b Incomplete—ambiguous external genitalia
3 With female ducts and male external genitalia
4 With nonvirilizing adrenal hyperplasia adrenal insufficiency and female external genitalia
5 Other forms

tial forms of the syndrome of feminizing testes suggests a genetically determined disorder An analysis by Grumbach and Barr of 16 pedigrees by the proband method showed a familial aggregation of affected cases consistent with either a sex linked or a sex limited dominant trait The action of the mutant gene is not known but it clearly results in partial fetal testicular insufficiency and perhaps in some enzymatic defect in the synthesis of testicular hormones In addition Wilkins has obtained suggestive evidence of end-organ insensitivity to androgen

Witschi Nelson and Segal have advanced the hypothesis that the mothers of affected males transmit an antitestis substance during pregnancy—possibly an antibody

Syndrome of Gonadal Dysgenesis

The typical form of this syndrome with its cardinal feature of a female phenotype rudimentary gonads sexual infantilism short stature and associated anomalies is well recognized About 80% of subjects with gonadal dysgenesis have male type nuclei and by inference a male sex chromosome

constitution In general chromosomal females have fewer of the associated anomalies Attention has recently been focused on the vagaries of this syndrome Variants have been described in which stature was normal the characteristic anomalies absent or the gonadal defect less complete In some instances a variable although usually minor degree of masculinization of the external genitalia has been noted in others there has been slight breast development or one or more menses Recently cases have been described in which the gonadal ridge contained a few vestigial seminif

TABLE 3—Syndrome of Gonadal Dysgenesis and Its Variants

	Chromosomal Male (Dysgenesis of Testes)	Chromosomal Female (Dysgenesis of Ovaries)
Complete	Syndrome of gonadal dysgenesis	Syndrome of gonadal dysgenesis
Incomplete variants	Gonadal dysgenesis with phallic enlargement	
	Gonadal dysgenesis with vestigial cortical development	Ovarian dysgenesis with vestigial medullary development
	Gonadal dysgenesis with male pseudohermaphroditism	Ovarian hypoplasia
	Turner's syndrome in boys and men	

erous tubules and ovarian follicle Whether these variants which form a clinicopathologic entity all have the same etiology has not been established A classification of the syndrome of gonadal dysgenesis is shown in Table 3

The etiology of this disorder although obscure has been the subject of considerable speculation Familial instances are rare In 1957 Grumbach and Barr found only 9 families in which more than one person was affected to these can now be added 4 other families Of interest is the consistency in the clinical stigmata within affected sibships occurrence of the disorder in identical twins and the preponderance of chromatin negative case

Seminiferous Tubule Dysgenesis (Klinefelter's Syndrome)

Since the first observations published in 1956 that some apparent males with Klinefelter's syndrome had female type nuclei a great deal of pertinent information has been accumulated rapidly Bernard Lennox's group in Glasgow has been especially active in this field It is now quite apparent

that the term Klinefelter's syndrome no longer adequately describes this group of patients. We have proposed the term seminiferous tubule dysgenesis since it indicates a disorder congenital in nature principally evident in the seminiferous tubules. Ther term carries no stigma of sex reversal and is equally applicable to persons with male or female nuclei.

Although early reports of the syndrome drew attention to endocrine manifestations such as gynecomastia and a variable degree of eunuchoidism, it is now recognized that the only essential features are the histologic structure of the testis and azoospermia or, rarely, oligospermia. Testes are usually atrophic but may be only moderately diminished in size. In most but not all patients excretion of urinary gonadotrophins is elevated. The increased incidence of mental deficiency in this syndrome has been stressed in recent reports. In surveys of mentally retarded males, Ferguson-Smith in Glasgow found 4 among 325 (1.2%) who were chromatin positive. In a similar study by Prader *et al.* in Zurich 2.4% of 336 mentally defective males had female nuclei.

The most significant estimate of the incidence of this disorder in an unselected group of phenotypic males is that recently reported by Moore (Lancet 1:217, 1959). A female chromatin pattern was observed in 5 of 1,911 newborn males tested for chromosomal sex at the Winnipeg General Hospital. Parenthetically, of the 1,804 female infants examined all had female-type nuclei. This strikingly high incidence (0.26% among males, 0.13% among infants of both sexes) is not inconsistent with a previous report from Glasgow which indicated that 17% of males with azoospermia were chromatin positive. The data on incidence clearly establish the chromatin-positive form of seminiferous tubule dysgenesis as the commonest type of human intersex and has an important bearing on the problem of male infertility.

The histopathology of the testis in seminiferous tubule dysgenesis is variable and in part dependent on the age at which the testicular biopsy is obtained. Morphologic differences between the gonads of chromatin-positive and chromatin-negative subjects with seminiferous tubule dysgenesis have been described. In a few of our cases the similarities in testicular appearance were notable.

It seems probable in the light of current concepts of gonadogenesis that in persons with seminiferous tubule dysgenesis and female type nuclei the failure of the embryonic cortical component to develop and to suppress the medullary component results in differentiation of the primordial gonad as a testis The cause of this defect in gonadogenesis is a matter of speculation Witschi Segal and Nelson have assumed that the primary defect is a degradation of the ovum possibly due to overripeness which results in a deficiency of germ cells However it is not clear whether the germ cells are deficient initially or whether they fail to multiply and develop after migration to the gonadal ridge There is evidence to implicate a genetic factor although again little support can be adduced for a simple genetic mechanism Sporadic familial cases and the occurrence of the disorder in identical twins have been described

A most interesting development has been the report of chromosome studies in a case of seminiferous tubule dysgenesis with female chromatin pattern Recent determinations of the chromosome number in human cells indicate that the diploid number is 46 (22 pairs of autosomes and 1 pair of sex chromosomes) Jacobs and Strong (Nature 183 302 1959) examined directly the chromosome morphology in specially treated cells from a specimen of bone marrow from their patient and found 47 chromosomes in cells at metaphase suitable for detailed analysis of chromosome morphology A Y chromosome was detected and also an extra chromosome of approximately the same size as the X and with similar morphologic characteristics This evidence suggested an XXY sex chromosome constitution Bone marrow preparations from the parents also were examined each had a normal chromosome number (46) and morphology Dr C E Ford (personal communication) has made similar observations in 4 additional chromatin positive patients with this syndrome with the exception that one showed a presumptive XXY/XX mosaic

Chromatin positive patients with this syndrome provide the first documented examples of a chromosomal aberration involving the sex chromosomes in man although an earlier report suggested it may also occur in true hermaphroditism

Several explanations for such a phenomenon can be ad vanced The apparent XXY sex chromosome constitution could be due to nondysjunction during gametogenesis in ei ther parent during the second maturation division in the ovum at the moment of fertilization or during early em bryonic development before the earliest stage when twin ning takes place by cleavage In the latter event these per sons might have a mosaic distribution of sex chromosomes in somatic cells The role which genetic and deleterious en vironmental factors may play in the etiology of the chromo somal aberration is not clear Undoubtedly in the light of this remarkable new lead considerable attention will be fo cused on this problem

The new data indicate that the gonadal defect in chroma tin positive seminiferous tubule dysgenesis is a consequence of an abnormal sex chromosome constitution which leads to suppression of the cortical element of the primordial gonad The fetal testes which develop bring about normal male dif ferentiation of the genital tract At puberty if the function of the Leydig cells is adequate male secondary sexual char acteristics develop Ferguson Smith has studied the testicu lar structure in 8 prepubertal patients Apparently tubular hyalinization does not begin until the onset of puberty It seems probable that the characteristic appearance of the testes in adolescent and adult cases depends on the continu ing action either directly or indirectly of pituitary gonado trophins after puberty on an inherently defective testis which before this time shows only subtle signs of an abnor mal histologic structure

O aries with a Male Chromatin Patt n

Ashley and Jones have lately described a phenotypic fe male with slight clitoral enlargement who was found to have ovaries female accessory sex structures and a male chroma tin pattern This case is the first example of normal appear ing ovaries in a person with male type nuclei and appears to be the counterpart of chromatin positive persons with seminiferous tubule dysgenesis Why apparently complete sex reversal occur more frequently in chromatin positive person is not understood

It seems probable in the light of current concepts of gonadogenesis that in persons with seminiferous tubule dysgenesis and female type nuclei the failure of the embryonic cortical component to develop and to suppress the medullary component results in differentiation of the primordial gonad into a testis The cause of this defect in gonadogenesis is a matter of speculation Witschi Segal and Nelson have assumed that the primary defect is a degradation of the ovum possibly due to overripeness which results in a deficiency of germ cells However it is not clear whether the germ cells are deficient initially or whether they fail to multiply and develop after migration to the gonadal ridge There is evidence to implicate a genetic factor although again little support can be adduced for a simple genetic mechanism Sporadic familial cases and the occurrence of the disorder in identical twins have been described

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Chromatin positive patients with this syndrome provide the first documented examples of a chromosomal aberration involving the sex chromosomes in man although an earlier report suggested it may also occur in true hermaphroditism

Finally in the clinical management of patients with sexual anomalies it is well to remember that sex chromosomes gonads genitalia and hormones are not in themselves absolute determinants of psychosexual orientation The major role of the sex of rearing in determining psychologic sex and the many factors—psychologic social anatomy of the external genitalia—which influence the establishment of gender role have been convincingly demonstrated in patients with intersexuality

Familial Occurrence of Ullrich Turner Syndrome Including Observations on Pterygium Colli Cryptorchism and Meigs s Syndrome in Two Brothers with Congenital Anomalies is discussed by J Misley and H Reinwein[8] (Kiel Germany) This syndrome is characterized by growth and sexual retardation pterygium colli and cubitus valgus If there is increased gonadotrophin excretion also the Ullrich Turner Albright syndrome is present However not all characteristic signs are necessarily present in every patient with the Ullrich Turner syndrome as illustrated by Case 1

CASE 1 —Girl 16 sister of the patient in Case 2 had not yet menstruated and had no axillary or pubic hair Pterygium colli and cubitus valgus were not present X rays showed delayed epiphysial closure Exploration revealed aplasia of the ovaries and hypoplastic external genitalia

In the Turner syndrome in the male the symptoms vary from patient to patient even to a greater degree than among females

CASE 2 —Boy 13 had a feminine appearance and no axillary or pubic hair The skull was normal No dental anomalies were noted The neck was short and the penis small Cryptorchism was present on the right and the testis was not palpable Permission for testicular biopsy was refused

Because of the variable findings the authors suggest that the terms Turner syndrome ovarian agenesis and ovarian dwarfism should not be used but that the condition be described as gonadal dysgenesis Philipp suggested the term cryptogenetic male hermaphroditism with rudimentary gonads

Besides the easily detectable external anomalies in gonadal dysgenesis the authors often observed concomitant dwarfism—incorrectly interpreted by some workers as pituitary

(8) D t b d W h sch 83 601 634 Ap 11 19 8

Corticomedullary Imbalance

A spectrum of corticomedullary imbalance during gonadal ontogenesis according to sex chromatin pattern is set forth in Table 4. The various types of intersexuality listed in the table share in common the persistence and development to a variable degree of one of the two gonadal elements—cortex or medulla—contrary to the nuclear sex. The mildest form of imbalance in chromatin positive persons is evidenced by true hermaphrodites with an ovary and an ovotestis and in chromatin negative persons by true hermaphrodites with a testis and ovotestis. Patients with seminiferous tubule dysgenesis and female nuclei and those with ovaries and male

TABLE 4—CLINICAL SYNDROMES ASSOCIATED WITH VARIATIONS IN CORTICOMEDULLARY IMBALANCE DURING GONADOGENESIS

Female Chromatin Pattern	Male Chromatin Pattern
A *Classic true hermaphroditism*	A *Classic true hermaphroditism*
a Ovary and ovotestis	a Testis and ovotestis
b Ovary and testis	b Testis and ovary
c Ovotestes	c Ovotestes
d Ovotestis and testis	d Ovotestis and ovary
B *Ovarian dysgenesis with vestigial medullary development*	B *Gonadal dysgenesis with vestigial cortical development*
C *Seminiferous tubule dysgenesis*	C *Ovaries with male chromatin* (Ashley Jones)

nuclei exemplify extreme forms in which there is apparent complete gonadal reversal.

The etiology of the corticomedullary imbalance may reside in alterations of ontogenetic processes by either genetic or environmental factors or both. A genetic mechanism for gonadal dysontogenesis is firmly implicated in seminiferous tubule dysgenesis. In any event the causal factor exerts its deleterious effect on the primitive gonad before the 8th week of embryogenesis.

A new and remarkable development in the investigation of intersexuality and one with broad implications has followed the application of cytogenetic technics to this problem. An unusual sex chromosome complex has already been detected in one form of intersex and undoubtedly others will be discovered. This new lead should contribute important information on the role of the Y chromosome in man, on the etiology of anomalies and on cellular function and genic action.

F g 63 (t p) —Wh ls of co n ct t f m mp rt t f La ge cell e nte r mall ll m t wa d pe [l y

F g 64 (bott m) —G m l t w th t ll g Ge m lls a e f le t d g l Jh c

(C rt) f B adb y J T d B g R C J Cl E loc l 38 1006-1014 S p ber 1958)

with a gonad in the broad ligament on the left suggested the possibility of true intersexuality Microscopically however the left gonad was so undifferentiated that neither ovarian nor testicular organization was evident

The anatomic abnormalities associated with gonadal dysgenesis are not predictable and can be established only by exploratory laparotomy

Ten Year Old Boy with Positive Chromatin Test is described by K G Bunge and J T Bradbury (State Univ of Iowa)

Boy 10 was referred for study because the genitalia were slightly below normal size Other physical findings and laboratory data were normal The gonads were examined under general anesthesia One measured 1 5×1 and the other 1 4×0 9 cm Both vasa deferentia and epididymides were present On incision the parenchyma of the gonad was yellow did not string and appeared to the surgeon much like that seen in Klinefelter s syndrome

Biopsy of the gonads showed that the tunica albuginea was well developed The septula were continuous with the tunica vasculosa and divided the parenchyma into lobules The interstitial spaces contained capillaries and scattered connective tissue cells All convoluted tubules were lined with sustentacular cells and had a basement membrane and a thin lamellated connective tissue wall Some tubules were larger and contained in addition germ cells with large spherical nuclei and abundant cytoplasm No progressive stages of spermatogenesis were present Mitotic activity was not evident in the germ cells but several contained tetrads Some of the larger germ cells were invested with a single layer of sustentacular cell

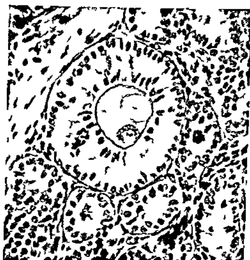
Occasionally a tubule had a dilated portion which contained an egglike body surrounded by a second layer of sustentacular cells (Fig 65) These ovular bodies were 60 120 μ in diameter and had a nuclear area which stained diffusely with hematoxylin and intensely with PAS and exhibited metachromasia with toluidine blue The cytoplasmic portion stained lightly with eosin was vacuolated or laminated and peripherally stained deeply with PAS

Darkly staining clumps of cells possibly exhibiting plasmagamy occurred in some tubules (Fig 65) Certain connective tissue septa contained cords of deep staining cells which were continuous with some of the convoluted tubules These cords had no basement membrane or lamellated connective tissue wall The cells contained deeply staining spindle shaped nuclei and scant cytoplasm It was not obvious whether these cords represented undifferentiated or degenerating tubules but several small egglike bodies were seen in them

The intratubular bodies were considered ova because (1) they had a nucleus (2) were of large size and contained

abundant albuminous cytoplasm (3) the outermost zone of the cytoplasm stained like a zona pellucida (4) the radial arrangement of the investing sustentacular cells resembled a corona radiata (5) oocytes have been described in seminal tubules of hermaphroditic sexually immature animals

Since the only known sex chromatin positive males have



F g 65 —Int at bul gg w th PAS p s t es e t c body d l g v cu l De p t ng p ph y D p t ng lu p f nu l betwee tw l f t nt l ll nd n dja t t t l (C tesy f B g R G d L db J T J U l 8 7 5 7 9 D mt 1957)

had the postpuberal syndrome of Klinefelter there is strong presumptive evidence that the syndrome will ultimately develop in this boy

Ovogonia in Rudimentary Gonads in Case of Turner s Syndrome with Male Sex Chromatin Pattern have been demonstrated by Robert B Greenblatt[3] (Med College of Georgia) thus lending further support to the possibility of complete sex reversal in humans This case represents the counterpart of the previously reported apparently paradoxical finding of spermatogonia in men with Klinefelter s syndrome and a female chromatin pattern

Girl 8½ exhibited typical Turner s syndrome Repeated smears of oral mucosa and blood showed a male sex chromatin pattern Urinary excretion of 17 ketosteroids was 3 8 mg /24 hours of 17

(3) J Cl Endocr 18 227 230 F b ua y 1958

hydroxycorticoids 6 9 mg and of gonadotrophin less than 6 6 m u The external genitalia were normal for a prepuberal female At laparotomy a rudimentary uterus and bilateral vestigial gonadal streaks were found Histologic study of the gonad revealed primordial follicles scattered through the cortex a small follicular cyst and small atresic follicles In one follicle a degenerating ovum was present and occasional seminiferous tubules lined with tall columnar epithelial



Fig 66—C aafi n f ll l w th d g t g m (*A*) nd mm t m f ou t b l (*B*) (C t y f G bl tt R B J Cl E doc l 18 2 7 30 F b y 19 8)

cells were observed at the periphery of the cortex (Fig 66) Leydig cells were absent in all sections examined

Turner s syndrome is one of the many syndromes with gonadal dysgenesis which have a common fundamental feature—rudimentary gonadal streaks In general these vestigial streaks are composed of stromal tissue without primordial follicles In a few instances primordial follicles and small follicular cysts have been reported This is the first case with primordial follicles and a female sex chromatin pattern

Sex Reversal Ovarian Tissue Associated with Male Nuclear Sex Gonadal dysgenesis Turner s syndrome is now a

well recognized though uncommon disorder of sexual development Its classic form is a female bodily habitus atrophic gonads absent secondary sex characteristics amenorrhea and increased urinary excretion of pituitary gonadotrophic hormones Often other congenital defects are associated short stature webbing of the neck and cubitus valgus The gonads are represented only by a primitive genital ridge of connective tissue and a few mesonephric remnants The cell nuclei of the skin and buccal mucosa contain no chromatin bodies indicating that the genetic sex is probably male D J B Ashley and C H Jones[4] (Liverpool) present a case with certain anomalous features which made it more analogous to the syndrome of testicular agenesis Klinefelter's syndrome than to gonadal dysgenesis

Baby age 10 days had labia majora and minora and a phallus suggestive of an enlarged clitoris with a hypo padiac urethra In front of the anus was a vagina with a second urethral opening on its anterior wall Urinary 17 ketosteroids were normal during the first 9 months of life Bone age at 18 months corresponded to chronological age At 17 months laparotomy revealed a uterus and fallopian tubes of normal size Both ovaries were in normal position slightly enlarged and cystic Biopsy showed a follicular cyst and many oogonia No testicular tissue was found Smears of the buccal mucosa were taken from both sides of the mouth on four occasions and a skin biopsy specimen was obtained The proportion of sex chromatin cells was consistently less than 6% well below the normal figure for normal females Blood films examined on three occasions revealed more than 6 drumsticks/500 cells

This case was confusing because at birth the infant appeared to be a female with an enlarged phallus a case of female pseudohermaphroditism The skin and buccal mucosa show male nuclear sex therefore she might be considered an instance of Turner's syndrome but the histologic appearances of the ovary present a serious discrepancy This is the only known case in which the gonad is histologically ovarian but the buccal and nuclear sex is male The embryogenesis in this case can best be explained as due to the ascendancy of an abnormal female evocator acting on the indifferent gonad in the earliest days of intrauterine life Failure of development of the gonad may not explain the etiology of this syndrome

(4) Lancet 1 4 6 Jan 11 1958

Gonadal Dysgenesis in Newborn Infant All cases of gonadal dysgenesis have in common rudimentary gonadal anlagen without germinal cells and female external genitalia. Ralph Richart and Kurt Benirschke (Harvard Med School)[5] report a case of a newborn infant with gonadal dysgenesis who underwent autopsy 19 days after birth. The gonadal histologic picture was unusual and one umbilical artery was lacking. Many typical features of the syndrome were present: webbing of the skin of the neck, edema of the hands and feet, normal female external genitalia and atypical hypoplastic gonads. Other anomalies were a fused kidney and adrenal gland, absence of one umbilical artery, tubular structures much like the testicular tubules of a normal male newborn, external genitalia with a hermaphroditic appearance, hypospadiac phallus, rudimentary uterus and fallopian tube on the left and on the right, in conjunction with the gonad containing tubules, a vas deferens. Sections of skin showed a male chromatin pattern.

It is suggested that development of a typical Turner syndrome in the male results from intrauterine injury to the fetus, with testicular maldevelopment as the primary cause of genital abnormality. Associated malformation may be explained by the concept of a teratogenetic termination period. Various agents producing an unfavorable intrauterine environment, such as viruses, drugs, toxins and hypoxia, may cause the syndrome of gonadal dysgenesis. The diverse congenital anomalies can best be explained on the basis of an effect on the whole organism at a critical period in development. The single umbilical artery may be one mechanism in the production of the syndrome.

In this patient the histologic appearance of the adrenal glands and accessory adrenal was normal. Apparently the androgenic activity of the human fetal adrenal is not capable of assuring male genital development in the absence of a normal fetal testis.

Renal Anomalies in Rudimentary Gonad Syndrome Raul Grinberg and Samuel Wais[6] report a case.

Woman, 23, was first observed at age 11 because of retarded growth. At the current admission she weighed 36.5 kg and was 140

(5) N w E gl d J M d 58 974 978 M 15 19 8
(6) M d B A 17 1 5 1 1 M y 19 7

cm tall On e trogen medication she had menstruated periodicall The breasts were developed and the areolae pigmented She had axil lary and pubic hair and the vulva appeared normal Laboratory studie showed positive results for gonadotrophin 96 units urinary smears were atrophic and 17 ketosteroids excretion was 14 mg /24 hours Renal function and blood calcium and phosphorus levels were normal Chromosome sex in neutrophilic blood cells (method of Davidson and Smith) was masculine the phenotype was feminine The patient also had color blindne s for yellow red and red

X rays of the urinary tract showed anomalies in both kidneys The right was larger than the left and slightly lower Both kidneys showed malposition being turned on their longitudinal axes Both pelves were irregular more so on the right Some calyces owing to rotatory change projected directly over the pelvis This was well delineated in films taken in the dorsal decubitus position In both kidneys the calyces were separated by intermediate pathways so that some appeared to empty directly in the pelvis

All patients with rudimentary gonads should be studied for urinary anomalies determination of chromosomal sex and changes in color vision since these factors might contribute to diagnosis in some difficult cases in very young patients

► [In this and in the following articles the term chromosomal sex has been used synonymously with chromatin sex pattern Actually I suppose the term chromosomal sex should be used only when the chromosomes have been identified A technic for recognizing chromosomes has been described by Ford (Nature London 178 1021 Nov 10 1956 ibid 181 1565 June 7 1958) Work now in press indicates that the chromatin blob of patients with seminiferous tubular dysgenesis may represent the XXY chromosome whereas the pattern in gonadal dysgenesis seems to be XO Of course no generalization is warranted until many cases have been studied by suitable technics —Ed.]

Infantile Dwarfism in Two Sisters Filiform Ovaries and Germinal Agenesis in One and Infantile Ovaries in the Other were verified surgically by J Vague C Miller J L Codaccioni and G Favier[7] (Marseilles)

Girls aged 20 and 15 had 2 older brothers and a sister 19 who were normally developed Another sister had died in infancy The older sister was 1 27 m tall and weighed 33 kg Distribution of fat was of the feminine type There were no signs of puberty The breast had not developed and the vulva was infantile Emotional orientation was also infantile The conjugal cartilages had not closed Major dystrophies were absent but the auricles were detached on both sides The EEG was essentially normal Assay of follicle stimulating hormone was positive 50 units urinary 17 ketosteroids measured 3 2 mg and pregnanediol 1 7 mg The sex chromatin pattern was feminine Operation revealed an exceedingly small infantile uterus

(7) Ann endocrinol 19 139 144 J Feb 1958

and tubes and flat ovaries about 3 cm long Several specimens from both sides showed characteristics of ovarian stroma but no evidence of germinal formation The pavilions of both tubes contained small calcarious noninflammatory granulations Administration of estrogens resulted in puberal development within a few weeks and some stimulation of growth The patient was lost to follow up a year after operation

The younger girl weighed 26 kg and was 1 3 m tall corresponding in size to that of a girl aged 10 or 11 Body conformation was feminine There was no evidence of puberty and cartilages were not closed X rays of the skull and visual fields were normal Follicle stimulating hormone could not be measured i e it was under 5 units The blood phosphorus level was normal Injection of 2 5 units of insulin reduced the fasting blood sugar level to 0 32 in 90 minutes without definite malaise The sex chromatin pattern was feminine Laparotomy revealed an infantile uterus and tubes The small ovaries were covered by a slightly thick pearly white substance A serous lentil sized cyst was opened in the right ovary Biopsies showed immediately beneath the white layer an infantile ovarian stroma with primordial follicles which were definitely more scarce than in the normal infantile ovary Treatment with gonadotrophins was prescribed but the patient could not be followed

The two syndromes described in the same family are thought to have different origins The hypophysial origin of infantile ovaries (Lorain syndrome) as seen in the second patient is generally accepted In view of the difficulty sometimes encountered in stimulating sexual development in patients with gonadal hypotrophy it is tempting to postulate some cause other than hypophysial insufficiency notwithstanding the fact that peripheral receptivity to hormones diminishes in proportion to the duration of their lack The coexistence of a germinal lesion and various dystrophies in the same family and the obvious reduction in primordial follicles suggest a primary dystrophy of the gonads which may perhaps range in degree between the normal state and agenesis

Seminiferous Tubular Dysgenesis

True Klinefelter Syndrome before Puberty is described by R Siebenmann and A Prader[8] (Univ of Zurich) The discrepancy between chromosomal and gonadal sex and the histologic gonadal findings in the true Klinefelter syndrome with female nuclear sex point to a disturbed gonadal devel

(8) S hw m d W h sch 88 607 610 J 21 1958

opment Elastic fibers are absent especially around many tubular scar remnants Since elastic fibers appear in the testicular canals only at puberty it would appear that tubular sclerosis sets in before puberty or it could mean that some of

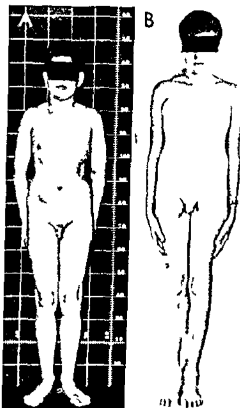


Fig 67—A bo ag d 11 B boy g d 1t B th pr p be l h w t ch 1 t po t Kln f lt y d nd th t ll m wh t e h d p po t and l ghtl f m body bu l l d m t (Court y f S he n R d P ad \ S hw m d Wch h 88 607 610 J e 21 1958)

the tubules do not participate in puberal maturing No previous observations have been made on prepuberal gonadal changes in the true Klinefelter syndrome

The authors studied 2 boys (Fig 67) aged 11 and 13 who did not present prepuberal signs but were recognized by chromosomal sex determinations as having true Klinefelter

syndrome. Clinically they showed slightly accelerated growth, somewhat delayed skeletal development and a feminine body build with an adipose thorax. Their progress at school was slow. The older boy presented pronounced eunuchoid body proportions. Secondary sex characteristics and gynecomastia were absent in both boys, which is not surprising at their age.

The nuclear sex as determined in both boys by oral mucosal smears and by skin biopsy in the younger boy was faintly female, the incidence of chromatin-positive cells being somewhat lower than in normal females. Such skin biopsy findings are characteristic of the Klinefelter syndrome.

Testicular histologic study showed a somewhat irregular tubular development but a normal amount of spermatogonia in the younger boy. In the other boy the tubular diameter had irregularly increased to prepubertal value, but spermatogonia had almost completely disappeared. Some scanty tubules showed hyaline sclerosis, but Leydig cells were still absent in both.

Since both boys showed other signs of the Klinefelter syndrome, it can be assumed that the typical tubular sclerosis of Klinefelter's syndrome with female nuclear sex begins only with puberty (probably before any increase in Leydig cells) but seems to be preceded by marked retardation or regression of germinal epithelium development.

Observations on Testicular Sex Chromatin Pattern in Male Infertility were made by Arthur R. Sohval and Joseph A. Gaines[9] (Mount Sinai Hosp., New York) on 37 infertile men to evaluate the incidence of infertility associated with the presence of a contrasexual chromatin pattern. Infertility was documented by oligospermia in 9 subjects and by azoospermia in 16. Seminal fluid could not be procured in 9 men with hypogonadism and in 3 others with psychogenic impotence. All testes were scrotal. Of 11 men with hypogonadism, 5 had Klinefelter's syndrome. Fresh testicular biopsy sections were fixed in Bouin's solution or formalin and stained with hematoxylin and eosin.

Typical sex chromatin bodies were found frequently in the Leydig cells of 3 of the 5 patients with Klinefelter's syn

(9) Fertil. & Steril. 9:334-34[illegible], July-Aug., 1958.

drome Sex chromatin bodies were not found in the other 34 patients

Discordance between chromosomal and gonadal sex may exist in the absence of hormone dysfunction with infertility as the sole or presenting symptom The absence of such divergence in 26 instances of uncomplicated (nonhypogonadal) infertility here reported suggests its relative infrequency However this should not deprecate the etiologic role of defective gonadogenesis in human male infertility It is suggested that sex chromatin studies be included routinely in the evaluation of male infertility of obscure or endocrine origin

► [As noted by Grumbach (see Special Article p 281) Stewart and co workers in Glasgow found a surprisingly high incidence of chromatin positive males (Lancet 2 117 July 19 1958) Prader and his associates have made a similar observation concerning mentally retarded boys in Zurich (Schweiz med Wchnschr 88 917 Sept. 20 1958) —E I]

Testicular Feminization

Testicular Feminization in Adults G A Hauser M Keller Th Koller R Wenner and F Gloor[1] (Univ Basel) studied 6 patients aged 19 52 Although the phenotype is feminine clinical diagnosis of this intersexform is facilitated by the following symptoms therapy resistant primary amenorrhea with sterility absence of sexual hair growth on pubes and axilla (hairless woman) missing or blind ending vagina absence of uterus and existence of inguinal hernia on both sides with palpable gonads (testes) The gonadal and chromosomal sex is masculine The values of excreted neutral 17 ketosteroids resemble those of normal men The estrogen output is diminished and follicle stimulating hormone levels are normal A distinct excretion of pregnanediol pregnanetriol complex can be found The estrogen effect in the vaginal smears and development of the breasts but not the other feminine characteristics are caused by testicular activity

The libido is that of a woman with orgasm and is compatible with a sexually satisfactory family life One patient experienced typical menopause with hot flashes at age 48 though she had never menstruated All patients had above average intelligence Since psyche and sexuality are unob

(1) Schwe med W h s h 87 1573 1590 D 8 1957

trusively feminine these persons should be reared accordingly The patients are informed only on the irreparability of amenorrhea and sterility They are allowed to marry

The authors advise against prophylactic surgical castration for prevention of possible malignant degeneration of the testes as it transforms healthy persons into patients with manifestations of endocrine deficiency

Owing to an increasing insufficiency of the testes and an increasing Jost effect (feminization in the male) different grades of masculine pseudohermaphrodites can be found The insufficiency effect starts in normal males and shows all the transitional stages including hypospadias testicular feminization and masculine dysgenesis of the gonads Testicular feminization is a true endocrinopathy in which the degree of testicular insufficiency can be gauged by the length of the vagina Histologically the testes show no degenerative changes—only failure in the development of the anlage This defect is proportionate to the degree of feminization of the male

► [This condition is being reported in proportions which are almost epidemic considering its previous rarity and the fact that the physician usually wishes to guard the anonymity of the patient I differ distinctly with the authors regarding the advisability of prophylactic surgical castration The incidence of malignant degeneration of the intra abdominal gonad in such cases has been truly alarming The symptoms of endocrine deficiency which the authors consider reason for avoidance of castration can be readily allayed by cyclic administration of estrogens —Ed]

True Alternating Hermaphroditism M Alvarez Coca M Aguirre G Gobeo and F Ferran report a case which appears to be the 12th of this type recorded in the literature

Patient 22 registered as a woman with completely feminine psychologic orientation sought treatment for an inguinal hernia Body build was quite masculine the voice was low and since age 18 the face had had to be shaved There was almost no mammary development Since age 15 the patient had been aware that she was abnormal and was therefore shy Fat distribution was feminine Examination showed a penile clitoris 7 cm long no labia minora and prominent labia majora The urinary meatus was feminine as was the vaginal orifice which was independent of it The vagina was infantile No prostate was palpable

Operation revealed an infantile uterus similar to that of a girl aged 10 and a left ovary which appeared normal for the same age The round ligament and depth of Douglas pouch were normal On the right side the round ligament was absent The inguinal canal was

( ) P b r doc 1 4 691 08 N D 1957

permeable with a hernial sac which reduced easily At the level of the right ovarian fossa was an oval mass which appeared to be a cyst an ovotestes or a testis In view of the patient s feminine psychologic orientation this was removed Histologic diagnosis was atrophic testis with partial spermatogenesis of primitive pha e without epididymis or vaginal tissue and with vestiges of testicular reticulum and perfect interstitial endocrine structure It was impos ible to obtain hormonal assays or to determine chromosomic sex

The authors believe that true hermaphroditism is a true embryopathy and that treatment should enhance the civil sex In the authors patient no ovarian biopsy was done be cause it was felt that removal of even a small part of the ovary might compromise its vitality and prove disadvan tageous Operation for right sided hernia favored removal of testicular tissue

► [This is a most amazing and unique case combining as it does the fea tures of testicular feminization with the presence of gonads of both sexe It provides a missing link between the syndromes of testicular feminiza tion and of true hermaphrodism —Ed]

True Hermaphroditism

Problem of True Hermaphroditism Clinical Morphologic and Somatotype Investigations in Two Cases were made by H H Stange K Rumphorst and K W Schaumkell[3] (Univ of Kiel) One patient aged 14 was chromatin positive She showed a special type of dysplasia bordering on gynandro morphism had a somatotype of 442 according to Sheldon s classification and was higher in gynandromorphy than the average 442 External genitalia corresponded to Overzier s type III Internal genitalia consisted of a small uterus (e cretory endometrial stage) a normal right fallopian tube and an ovary with a fresh corpus luteum The left adnexa which were in the hernial canal showed a rudimentary tube and a bean sized ovotestis the small rudimentary tube covered the te ticular tissue like a cap There were no x ray or hor monal abnormalities

The second patient aged 15 was chromatin negative and showed a dysplastic type (masculinism) The somatotype was 442 and lower in gynandromorphy than the average 442 External genitalia corresponded to Overzier s type II Internal genitalia consisted of a walnut sized uterus with normally placed but thin tubes In place of the right ovary

(3) Deutsche med Wchnschr 8 1860 1863 Nov 1 1957

a germinal fold as thick as a knitting needle which histologically proved to be a rudimentary ovary. The left side showed a morphologically similar germinal plate but attached to its lateral pole was a cherry sized testis with a hypoplastic epididymis. Urinary excretion of gonadotrophic hormones was markedly increased but that of the 17-ketosteroids was normal. X-ray studies showed no abnormalities.

The appearance of the genitalia of both hermaphrodites is interpreted along the lines of Overzier as the result of mixed permanent inductions. The hormonal activity of the gonads does not seem to determine the psychic orientation in true hermaphrodites. This is influenced more by genetic or social surroundings and upbringing. The authors' patients behaved according to their rearing, showed no eccentric behavior, were introvert and had no apparent emotional conflicts.

Therapeutically, the final sex assignment should not be decided by somatic and morphologic status alone but also by psychologic factors, sexual inclination and the patient's desire. Therefore, in the first patient, who had functioning internal female genitalia, corrective surgery was performed to facilitate male adjustment. In the second patient, with female emotional inclinations, the testis, rudimentary germinal plate and enlarged clitoris were amputated. The enlargement of the rudimentary vagina was postponed to a later, more favorable date.

Unilateral True Hermaphroditism. Two Cases with Sex Chromatin Positive Cellular Pattern are reported by Ira M. Rosenthal, Joseph H. Kiefer, Elizabeth McGrew and I. Pat Bronstein[4] (Univ. of Illinois). Each had an ovotestis on one side and an ovary on the other. Figure 68 shows a microscopic section of the ovotestis removed from 1 patient. Two thirds of the tissue consisted of testicular tissue and one third ovarian tissue. The ovarian tissue had dense stroma and many immature follicles. There was relatively sharp demarcation between the ovarian and the testicular tissue except at one point where immature follicles and tubules were noted side by side. The seminiferous tubules were small and widely scattered but cellular. There was no spermatogenesis. In the

(4) Pediat. 20:1006-1019, Dec., 1957.

testicular part of the section were cleftlike structures lined by cuboidal cells resembling the straight ducts of the testis Farther from this were ductlike structures lined by columnar cells that resembled epididymis The fibrous stroma of the testis was fairly cellular in areas, but no definite Leydig cells were recognized

In these patients the genitalia were developed along female lines except for the presence of the phallus in both and



Fig 68—O t st \ g o nf t w th rtex t n g m y p m d l f l l cles Pl p rt o of field te t c l t b les below H m t xyl e ed d f m ×6 (Co rte y f R enth l I M t / Ped t ics 0 1006 1019 D embe 1957)

of a urogenital sinus in 1 In neither was there evidence of vasa deferentia seminal vesicles or prostate Each was sex chromatin positive and thus the genetic sex was presumably female True hermaphrodites may be sex chromatin positive or sex chromatin negative as determined by skin biopsy Female sex was assigned to each child after careful consideration of all factors In each appropriate surgery was performed on the gonads and genitalia

The authors stress that to obtain optimal psychosexual development patients with intersexuality should be studied diagnostically in infancy so that definitive unequivocal as

signment of sex can be made before the gender role i e tablished

True Hermaphroditism Report of Case of the lateral type is presented by Walter Hughes Cyrus C Erickson Walter Flei chmann and James N Etteldorf (Univ of Tennes ee)

In patient 15 a cystic atrophic ovary was found in the left ad nexa a normal left fallopian tube a small uterus and an atrophic te



Fg 69 (Co rt y f Il gh W t l J I d t 52 66 669 Ju 1958)

tis in the right side of a bifid scrotum Figure 69 shows the patient had bilateral breast enlargement characteristic of a female with body build and external genitalia resembling a male The patient al o had a small phallus hypospadiac urethra and labia re embling the scro tum Skin specimens from various portions of the body each re vealed a male chromosomal pattern Two months after removal of the female organs bilateral mammoplasty was performed Over 8 months three stage repair of the hypospadias produced a penile urethra The vaginal cavity was not removed No hormone therapy was deemed necessary

Serious psychologic complications were avoided because

(5) J Ped t. 52 662 669 J n 1958

this patient was consistently reared as a boy despite the fact that he had ambiguous external genitalia from birth

True Hermaphrodite Siblings This report of true hermaphroditism in bilateral type in siblings presented by W A Milner W B Garlick A J Fink and A A Stein (Albany N Y) is believed to be the first in the literature

CASE 1—Boy 13 tall slender well developed showed early pubertal male hair escutcheon android type pelvis and slight breast enlargement A small testis was palpable in the left inguinal canal but it was not possible to bring it down to the scrotum manually The right testis was in the scrotum and presented a pea sized nodule palpable on the upper pole The penis was of normal size there was a balanitic 1 degree hypospadias with a narrow scrotal raphe band extending to the base of the penile shaft Cord structures and the prostate on rectal examination were small but intact Biopsy of the upper pole of the right testis revealed typical ovarian stroma containing some ova and developing graffian follicles that merged with well developed testicular tissue Biopsy of the lower pole of the left gonad disclosed ovarian stroma adjacent to the testicular tissue Examination of the pelvis did not reveal any female structures A skin biopsy taken for chromosomal sex determination was interpreted as consistent with the male sex

CASE 2—Boy aged 15 months brother of Case 1 was normal on physical examination except for anomalous appearing external genitalia The scrotum was small and ill defined on the left it contained a small retractile testis and on the right in addition to a palpable gonad a communicating hydrocele and indirect inguinal hernia The penis was small with a severe chordee and a hypospadiac urethra existing at the penoscrotal angle A nodule removed from the upper pole of the right testis was shown to be composed of ovarian stroma with many ova (Fig 70) A nodule from the upper lobe of the left testis showed typical ovarian parenchyma and immature testicular tissue (Fig 71) On exploratory laparotomy no internal female sex organs were found A skin biopsy for sex chromatin pattern was negative i e male Final diagnosis in view of a proved ovotestis only on the left side was true hermaphroditism unilateral type It is considered probable that the remaining portion of the right gonad was testis and that this patient also is representative of the bilateral type of true hermaphroditism Hypospadias repair is planned in a few years and androgen supplement will be used if needed at puberty or earlier

The authors conclude that surgical sexual gonadal separation in most ovotestes is feasible and histologically complete as was true in the 2 cases reported The finding of true hermaphrodite siblings has given indirect support to the geneticists in their controversy concerning the cause of this condition

(6) J U 1 9 1003 1019 Ju 1958



F g 0 (top) — od) from pp j le of ɡl t te t s composed f s an t a wnb ma y f luced f m × l J
F g 71 (bott m) — Nod l f m urpe p l f l ft t t h w d typ l f hym l mmat t t lar t d d f m 120
(C t y f M lne W A t I J U l 79 1003 1009 J e 1958)

GONADOTROPHINS

Urinary Excretion of Interstitial Cell and Follicle Stimulating Hormone Activity during Normal Menstrual Cycle was studied by Janet W McArthur Jane Worcester and Francis M Ingersoll (Boston) Changes in the day to day excretion of interstital cell stimulating hormone (ICSH) were determined qualitatively throughout 17 menstrual cy

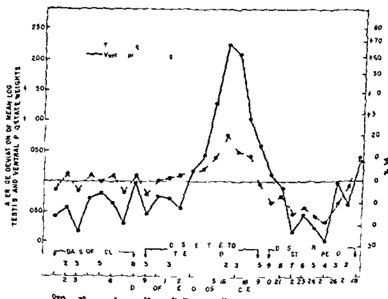


Fig 2—Composite 28 day cycle rep ... (Courtesy of M Arthur J ... J Clin Endoc ... 18 1186 1201 November 1958)

cles in 13 normal adults by a technic depending on repair of ventral prostatic atrophy in the hypophysectomized immature male rat Changes in the excretion of follicle stimulating hormone (FSH) were estimated from concomitant changes in testicular weight

Composite curves were derived by summating the average deviations from the mean of each individual cycle according to (1) the days of the cycle (2) the days preceding or following the day of minimal basal body temperature and (3) the days before the next menstrual period (Fig 72) A strik

( ) J Clin Endocrin 18 1186 1201 November 1958

ing parallelism was noted between the changes in the weights of the ventral prostate and testis It appears that the cycle is characterized by (1) erratic and with one exception insignificant fluctuations in both FSH and ICSH excretion during the follicular phase of the cycle (2) increase in level of excretion of both hormones which begins and may possess biologic significance before the thermal nadir the levels attaining statistical significance the day after the thermal nadir and remaining appreciably above the baseline for 4 days (3) a progressive trend downward which reaches significantly low levels toward the close of the luteal phase and (4) a subsequent trend upward during the premenstruum which fails to attain statistical significance

The quantitative relations between day to day variations in the weights of the ventral prostate and testis were examined by computing regression equations expressing the composite change in prostatic weight/unit change in testicular weight

It is concluded that the normal menstrual cycle is characterized by (1) a midcycle peak period of FSH and ICSH excretion during the early phase of which there is a change in the ratio of ICSH to FSH and a transient preponderance of ICSH with onset of the midcycle peak being closely related in time to the shift in basal body temperature (2) a late luteal trough followed by a rising trend in the excretion of both hormones beginning toward the end of the luteal phase and continuing into menstruation

Studies on Biologic Characterization of Human Gonadotrophins III Comparison with Sheep Follicle Stimulating Hormone by assays using the simultaneous response of the uterus and ovary of the intact rat was made by A Albert and Shirley Kelly[8] (Mayo Clinic and Found) The parameters of the assays showed that the ovarian response to human pituitary gonadotrophin (HPG) was three times that to follicle stimulating hormone (FSH) and the uterine response to HPG was two and a half times that to FSH The dose ratios showed that HPG was twice as effective as FSH in inducing secretion of estrogen The ovarian response to both FSH and HPG was a linear function of the log of the dose The uterine response to HPG also was a linear func

[8] J Cl E d 1 18 1216 122 N be 1958

tion of the log of the dose but the response to FSH was not. It was concluded that HPG is not identical with FSH and that the widespread use in clinical literature of the term urinary FSH for an assay of HPG is incorrect.

Bioassay of Various Gonadotrophins was performed by Michael Apostolakis and Klaus Dieter Voigt[9] (Hamburg). Sheep interstitial cell stimulating hormone (ICSH), human follicle stimulating hormone (FSH), human menopausal gonadotrophin (HMG), pregnant mare serum gonadotrophin (PMS) and human chorionic gonadotrophin (HCG) were tested by ventral prostate weight increase tests in intact (VPWI) and hypophysectomized (VPWH) immature rats, ovarian weight increase tests (OW) in intact immature rats (with or without an HCG augmentation dose) and the weaver finch test (WF).

For ICSH and HCG the VPWH test is the most sensitive; the VPWI test, however, gives almost as good results when used in assaying HCG and is much less time consuming. For PMS the OW test is more sensitive and accurate than the VPWI test, responding over a wider dosage range. Human menopausal gonadotrophin was tested only by the VPWH test to ascertain its ICSH-like activity. Threshold doses of the foregoing gonadotrophins in the WF test were determined. With the HCG augmentation test, human FSH showed an activity comparable with that already reported for animal FSH. Preliminary investigations on HCG recovery from human urine reveal the superiority of the VPWI test when used for this purpose. The recoveries were equally good after kaolin absorption and alcohol precipitation.

Clinical Routine Method for Quantitative Determination of Gonadotrophins in 24 Hour Urine Samples is described by Svend G. Johnsen[1] (Copenhagen). The method is based on the extraction of substances with gonadotrophic activity from a tannic acid precipitate by means of ammonium acetate-ammonium hydroxide-alcohol mixtures. Hyflo supercel is used to support the tannic acid precipitate as a thick filter cake on a Buchner funnel. The filter cake acts as a column for countercurrent differentiation and elution. The equip-

(9) Acta endoc. [illegible] 8 54 (8 May 1958)
(1) Ibid. [illegible] 69 88

ment needed is simple and inexpensive and the method is rapid and well suited to clinical routine assays in nonspecialized laboratories

The extracts contain several times less inert material than those obtained in other methods, are devoid of free and protein bound tannic acid and are highly soluble and free from estrogens and augmenting substances. The toxicity of the extracts for immature mice is low and the method allows the same quick procedure to be applied to specimens with high or low titers

Recovery experiments and repeated assays on pools of urine revealed a high degree of consistency of results. In 2 subjects a remarkably constant gonadotrophin excretion from day to day was found with this method. The authors suggest that the day to day variation in gonadotrophin excretion reported by others may be attributed to errors in the extraction methods used

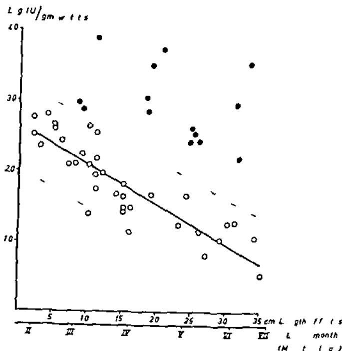
Chorionic Gonadotrophin in Hydatidiform Moles The curve of human chorionic gonadotrophin (HCG) in placental tissue throughout gestation closely resembles that of HCG in pregnancy serum or urine indicating that the level of HCG in these fluids probably reflects the release of the hormone by the placenta. The pathologic transformation of the chorion known as hydatidiform mole is frequently—although not invariably—associated with greatly elevated serum and urinary levels of HCG. L. Diczfalusy, L. Nilsson and A. Westman (Karolinska Hosp., Stockholm) studied the concentration of HCG in 14 verified moles and compared the results with those of 11 placentas that were obtained from apparently healthy abortion cases at various stages of gestation

In pregnancy the peak period of high HCG concentration is short. From the 5th month of pregnancy onward the placental concentration of HCG is below 20 I.U./Gm tissue

Some of the moles had HCG concentrations far above those found in normal placentas. When the logarithms of placental HCG concentration (log I.U./Gm wet weight) were plotted against the length of the fetus (or menstrual age) a statistically valid straight line could be drawn. The

( ) Acta [illegible] 28 13 14 J 1958

regression of log concentration HCG against length of fetus was highly significant When the log potencies of HCG in moles were also correlated with the approximate menstrual age and related to placental estimates (Fig 73) the lines delineated the fiducial intervals within which 95% of normal



Fg 73 —k g f pla t l c c nt t n (log I U /Gm. t w ght) f human ch n c g d t oph (HCG) g in t l gth of f t (pen l) Eq t f l e mputed s Y = 64—0 056 x whe x l ngth of f t t m ter d Y l g conc ntr t on of HCG Brok n l es b nd c al ng th wh h 95% of ndi d l s r ults pect d to fall S l d l s d te lt f HCG ys hydat d f rm m l (Court y f D c f l y E t al A ta lo- l 8 137 147 J 1958)

placental concentrations might be expected to fall Placental HCG above 1 500 I U is unlikely Overlapping between placental and mole HCG values entirely disappears when the moles are arranged according to the length of gestation With advancing duration of pregnancy urinary or serum assays of HCG offer a constantly improving aid in differential diagnosis of hydatidiform mole

CONTROL OF GONADOTROPHIC SECRETION

Direct Effect of Estradiol on Pars Distalis was studied by S. Ko e and J. I. Nelson[3] (Univ. of Melbourne). A micro-injector technic was used to infuse with estradiol male rats that had been castrated for 7-8 months. The infusion was made directly into the hypophysial fo sa, just outside the hypophysial fossa or subcutaneously. Infusion of estradiol directly into but not outside the hypophysial fos a depressed the castrate changes in the gonadotrophs of the pituitary over 7-10 times more than did the same do e when given systemically. A graded response from the anterior to the posterior edge of the pituitary was sometimes observed when estradiol was infused into the anterior edge of the hypophysial fossa.

The e results support the theory that estradiol has a direct effect on the pituitary and influences gonadotrophic hormone production and release.

Early Puberty Related to Cerebral Tumors. Marcel David, J. de Ajuriaguerra and A. Bonis[4] report 1 case due to chorio-epithelioma of the pineal body confirmed at autopsy and other ca es observed clinically.

CASE 1.—Boy aged 7 years 8 months was hospitalized. He ha l be gun to show abnormally rapid growth 8 *months* before with development of the penis, pubic hair and deepening of the voice. Shortly before admission he had ha l unexplained fever for 8 days which responded to antibiotics. After a vaccination, vomiting, hea lache and somnolence ha l appeared. Intracranial pre sure wa evident on admission. Blood sugar level was 132 mg./100 ml., urinary 17-ketosteroids 10 mg./24 hours, prolan B in the serum over 200 r.u. but unit, estrogen 124 µg./24 hours (level of a pregnant woman at 6 weeks). X-ray f the kull showe l decalcificati n of the qua lrilateral lamina and calcification of the pineal region lightly left of the midline. Encephalography showed dilatati n of the lat ral v ntricles and extreme dilatation f the 3d ventricle with a c nvex notch just in front t the posterior part. An attempt was ma l to remove the tumor with radioactive gold. Immediate re ults were favorable but later malignant exten ion t the eyelid and evidence of vi ceral metastases w r note l. He die l months after appearance of the first cerebral s n

Autopsy showed the pineal tumor and cerebral, pulmonary r and hepatic meta tases. The pineal le i n remained localize l in the retro peduncular region and seemed to be retracted by the r t ti n

(3) ... J. E. ... I. & M. S. 35: 0 610 D... be ...
(4) S m ... h p P ... 33: 1935 1958 N ... 1957

effect Serial sections of the 3d ventricle showed no invasion or metastases Recent hemorrhagic metastases were noted in the left prefrontal region the paracentral lobule and the occipital lobe The pineal tumor was classified as teratomatous but the metastases showed chorioepithelioma

The other cases were all in boys Early puberty occurred in an imbecile aged 10 who had had convulsions in infancy but encephalography showed only slight ventricular dilatation with no evidence of tumor Sudden rapid growth and puberal changes appeared in a boy aged 11 during recurrence of a medulloblastoma that had been operated on 3 years previously Precocious puberty appeared 4 months before intracranial hypertension due to a tumor of the posterior portion of the 3d ventricle in a boy aged 7 Early puberty and diabetes insipidus occurred in a boy aged 8 a year before intracranial pressure symptomatic of a tumor of the 3d ventricle was noted Rapid growth without puberal signs were symptomatic of a tumor of the pineal region in a boy aged 5

These experiences and a review of the literature lead the authors to conclude that there are three different types of sexual precocity of neurologic origin with supposedly different mechanisms (1) Puberty of hypothalamic origin is caused by excitation of stimulating centers of the anterior hypophysis or by destruction of hypothetic structures which inhibit them as observed in infections hydrocephaly tumors of the 3d ventricle and some epiphysial tumors The normal histologic appearance in almost all verified cases suggests a direct influence of hypothalamic sexual centers on the gonads but some recent observations have demonstrated a hypophysial relay by increase in follicle stimulating hormone at least in some cases (2) Precocious puberty of epiphysial origin in the male is of uncertain mechanism—suppression of a hypothetic purely endocrine secretion or removal of neural inhibition by the diencephalon and hypophysis or of a direct inhibition of the gonads by the epiphysis (3) Teratomatous hormone secreting tumors of the pineal region are a reality and the mechanism is certain

It should not be surprising that uncertainty is encountered in study of pathologic puberty since many questions remain about the mechanism of physiologic puberty Only detailed study of additional cases including elimination of sexual stimulants and derivatives of sexual hormones them

selves and minute anatomic investigations will ultimately resolve these problems

► [Since intracranial lesions of all sorts can produce precocious puberty, it is not clear whether the early puberty associated with intracranial choriocarcinomas should be attributed to hormonal activity of the tumor. I have seen only one such case and in it there was no clue as to whether the site or the hormone was responsible.—Ed.]

Hormone Excretion in Precocious Puberty in Girls. 11 patients aged 7 months to 10 years was compared with that in 15 normal controls aged 3-10 by R. D. Bulbrook, F. C. Greenwood and A. H. Snaith (London). In the 15 normal girls no estrogen was detected in the urine with 1 exception, a girl aged 7 who excreted 2.9 µg./24 hour. In girls over age 11 who had breast development and pubic hair but who had not menstruated measurable amounts of estrogen were found (2.9-7.1 µg./24 hours). Estrogen excretion, 17-ketosteroid excretion, gonadotrophin excretion and the grading of the vaginal smears of those with early puberty are shown in the table.

In contrast to the controls, 9 of the patients were excreting estrogen above 1 µg./24 hours. In 7 patients, positive vaginal smears were correlated with the finding of estrogen in the urine and in 3, negative smears were correlated with absence of estrogen. In a patient aged 7 months, a negative smear was obtained in conjunction with 1.6 µg. of urinary estriol, whereas in a patient aged 6 a positive vaginal smear was obtained but no estrogen was detected in the urine. Although the number of patients was too small for statistical analysis, there appears to be a good association between the vaginal cytology and estrogen output although the latter is low (2.0-6.8 µg. total estrogen/24 hours).

The results indicate that girls in whom certain of the secondary sexual characteristics, advanced growth, breast development and pubic hair, have developed but in whom regular menstrual cycles have not been established, the excretion of estrogens is much less than that in adult women. It is not known whether the estrogen excreted by girls with precocious puberty is of adrenal and/or ovarian origin. Estrogen excretion is nevertheless almost certainly greater in this group than in normal girls without any signs of approaching puberty. A dramatic rise in estrogen excretion

(5) A. D. Ch hood 33 95 300 A gu t 19 8

Estrocen 17 Kftosteroid Gonadotrophin Excretion and Vaginal Smear Findings in Girls with Precocious or Early Puberty*

C N	Ag (y)	Oe t e	O t dol	O st l	T t l (μg / 4 h)	V gi l Sm	17 k t te d (mg / 4 h)	Gon d t ph s (/ 4 h)
1	7/12	0 0 0 0	0 0 0 0	0 0 1 8	0 0 1 8	N gat N g t e	0 7 (0 47 0 16)	N g u N gat
2	1 10/12	0 0 1 1	0 0 0 0	2 2 4 2	2 5 5	Po t Po t e	2 5 (1 38 ± 0 66)	Neg t N g t
3	2	1 8	0 0	3 4	5	P t	1 6	—
4	6/12	0 0	0 0	0 0	0 0	N g t	0 9	N gat ve
5	6	0 0	0 0	0 0	0 0	P t e	1 (2 3 ± 0 85)	Negat e
6	8 6/1	0 0 1	0 0 0 0	0 0 0 0	0 0 1 2	N g t e Neg t	4	Negat
7	10	3 8	0 0	3 0	6 8	P t e	3 7	Po t e
8	8	1 9 0 1 1	2 1 0 0 0 0	1 7 1 4	5 7 4 1 5 5	P t	4 4	N g t N g t e Neg t
9	10	0 0 1 4 0 0 0 0 0 0 0 0	0 0 1 0 0 0 0 0 0 0	0 0 2 1 9 5 1	0 0 4 6 1 9 5 1	P t e	4 1	P t e 5 0 5 0
10	10		S F g t		11 38	P t	5 1	N g t 5 0 10– 0
11	10 10/12		S F g 1		2 6–29	Po t e	7 1	10 20

F x 1 k t g n m l 17 k t t d t g l g g p 0 1 1 5 5 10

occurs with the appearance of regular menstrual cycles undoubtedly of ovarian origin Therefore estrogen 17 ketosteroid and gonadotrophin determinations carried out on single 24 hour specimens are not diagnostic of precocious puberty because completely normal values are not incompatible with the diagnosis Nevertheless the results clearly show that estrogen excretion is usually raised above control levels associated with a positive vaginal smear

A more sensitive method than is now available which could differentiate with certainty between control levels and the small amounts of estrogen generally found in precocious puberty might be of diagnostic use Even with the present method of Brown the results are useful especially in conjunction with the 17 ketosteroid values because if a gross pathologic condition in the gonads or adrenal cortice exists the figures will probably be high i e well within the adult range This is unlikely in precocious puberty except when the periods are well established and not infrequent

► [The methods used here are among the very best now available Even so as the authors properly point out amounts in the urine of less than 5 μg per estrogenic compound per day cannot be measured with any degree of accuracy Of particular interest and in distinct contradiction to earlier reports is the lack of gonadotropin in the urine of patients with idiopathic constitutional or hypothalamic precocious puberty —Ed]

GONADAL HORMONES

Gestagenic Hormones in the Organism are discussed by *Josef Zander*[4] (Univ of Cologne) Progesterone is not the only naturally occurring steroid with gestagenic activity Two of its metabolites Δ^4 3 ketopregnene 20α ol and Δ^4 3 ketopregnene 20β ol (Fig 74) have shown biologic activity in both the Hooker Forbes and Clauberg test

The occurrence of gestagens in the ripe follicle about 2 days before ovulation is evidence that the steroids are produced in the human ovary before ovulation The highest concentration of gestagens in the corpus luteum is produced between the 7th and 8th days after ovulation The relatively high amounts of gestagens present in the placenta by the 2d month of pregnancy are evidence that this organ plays an early role in production of these compounds Their total amount increases from the 2d to the 10th month of preg

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ESTROGEN 17 KETOSTEROID GONADOTROPHIN EXCRETION AND VAGINAL SMEAR FINDINGS IN GIRLS WITH PRECOCIOUS OR EARLY PUBERTY*

C e N	Ag (y)	Oe t o	O t d ol	O str l	T t l (μg / 4h)	Vagin l S ear	17 k to t r d (mg / 4 h)	G n d tr ph n (u / 4 h)
1	7/12	0 0 0 0	0 0 0 0	0 0 1 8	0 0 1 8	Negat N g t e	0 7 (0 47 ± 0 16)	N g t e Neg t
2	1 10/12	0 0 1 3	0 0 0 0	2 2 4 2	2 5 5	P t Po t e	2 5 (1 38 ± 0 66)	N g t N g t e
3		1 8	0 0	3 4	5 2	P t	1 6	—
4	6/12	0 0	0 0	0 0	0 0	N gat e	0 9	N g t e
5	6	0 0	0 0	0 0	0 0	P t	1 (? 3 0 85)	Negat
6	8 6/12	0 0 1	0 0 0 0	0 0 0 0	0 0 1	N gat e N g t	4	Negat e
7	10	3 8	0 0	3 0	6 8	P t	3 7	Po t
8	8	1 9 0 1 3	1 0 0 0 0	1 7 2 1 4	5 7 4 1 5 5	P t	4 4	Negat e N g t e N gat
9	10	0 0 1 4 0 0 0 0 0 0	0 0 1 0 0 0 0 0 0 0	0 0 1 9 5 3	0 0 4 6 1 9 5 1	P t e	4 1	P 1 5 0 5 0
10	10		S F g 1		11 38	P t	5 1	N g t 5 0 10 20
11	10 10/12		S e F g 1		6 29	Po	7 1	10 21

F b 1 k t g n 1 17 k t t d t g 1 g g 1 0 1 1 5 5 10

Progesterone is inactivated mainly in the liver and to a lesser degree in the kidneys and peripheral tissues such as muscle Metabolites are excreted from the liver via the bile and the hepatic vein and through the latter route into the urine Animal experiments indicate an enterohepatic circulation for progesterone

Δ^4 3 Ketopregnene 20α OL and Δ^4 3 Ketopregnene 20β OL Two Naturally Occurring Metabolites of Progesterone Isolation Identification Biologic Activity and Concentration in Human Tissues are reported by *J Zander T R Forbes A M von Munstermann and R Neher*[7] After extraction and distribution between various solvent these compounds can be isolated by paper chromatography in a 70% methanol n hexane system Both have been isolated from human ripe follicles corpora lutea placentas and fat tissue and have been shown to be metabolites of progesterone Δ^4 3 Ketopregnene 20α-ol had one half to one third the progestational activity of progesterone and Δ^4 3 ketopregnene 20β ol was one fifth to one tenth as active Both compounds have progestational activity by the Hooker Forbes and Clauberg tests and are therefore to be regarded as gestagens

Both isomers but chiefly Δ^4 3 ketopregnene 20α ol are present in placentas between the 2d and 10th months of pregnancy The values indicate an average placental progesterone Δ^4 3 ketopregnene 20-ol fraction ratio of 5 8 1 Progesterone was detected in all of 7 follicles obtained 1 or 2 days before ovulation In 6 of them the combined Δ^4 3 ketopregnene 20-ol fraction was also found In 25 of 28 corpora lutea of the cycle the Δ^4 3 ketopregnene 20 ol fraction was present

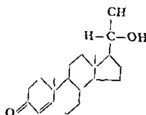
Only progesterone was detected in the corpus luteum of the 3d day of menstruation No progestational material was found in older corpora lutea

In 12 of 19 corpora lutea of pregnancy the Δ^4 3 ketopregnene 20 ol fraction was detected Neither the concentration of progesterone nor that of the Δ^4 3 ketopregnene 20 ol fraction in the first third of pregnancy was higher than their levels during the secretory phase of the menstrual cycle

J Clin Endocr 18 337 3 Ap 1958

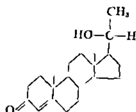
nancy Progesterone has been quantitatively estimated in peripheral blood uterine vein blood and umbilical vein blood at term From these values it is possible to calculate the amount of progesterone coming from the placenta to the mother Relatively high concentrations of progesterone also pass from the placenta to the fetus There is some indication that the pathway of progesterone metabolism in the mother differs from that in the fetus

It is assumed that progesterone develops in the steroid producing glands from acetate and cholesterol The first member of the group of steroid hormones thus produced is Δ pregnene 3β ol 20 on The latter compound is transformed into progesterone by the enzyme 3β ol dehydrogenase The enzyme is present in all



1 3 Ketopregnen 20α ol

F g 74—B ynth i f g t g h (C urt y f Za de J C b rt h F ih 17 8 6 895 O t l 1957)



1 3 Ketopregnen 20β ol

steroid producing organs i e the corpus luteum placenta testis and adrenal cortex and is absent from all other tissues It has been shown that testosterone may be transformed into estrogens by enzymes of the human ovaries In vivo studies have indicated the transformation of cholesterol into estrogen in the human body The authors isolated Δ^4 androstene 3 17 dione a steroid with androgenic activity from corpora lutea

All these observations seem to imply that biosynthesis generally occurs along the same lines in the various sex hormone producing tissues The predominance in the production of certain hormones by certain tissues and under various physiologic conditions is probably due to quantitative and not qualitative differences in the function of the respective enzyme systems Thus the formation of gestagens androgens and estrogens need not be considered any more as different biochemical processes but may be viewed as interdependent biochemical functions

gesterone may offer clues as to the function of various portions of the progesterone molecule Neosteron appears to be a good progestational compound with minimal androgenicity Nilevar® appears to be the best anabolic agent Norlutin and Enovid demonstrate good progestational activity with minimal anabolic effect

► [Because of the multiplicity of their hormonal actions 19 nortestosterone derivatives may produce unusual endometrial pattern It is of particular importance that the clinician and pathologist be familiar with them to avoid unnecessary hysterectomies —Ed]

Catabolic Effect of Dihydrotachysterol and Anabolic Action of 17 Ethyl 19 Nortestosterone on Uptake of Radiosulfur in Healing Fractured Bone of the Rat was investigated by K Kowalewski[9] (Univ of Alberta) The technic of measuring uptake of radiosulfur (S^{35}) in a healing fractured humerus of the rat is based on the established observation that the selective deposition of radiosulfur in certain tissues is due to the utilization of sulfate ions in the synthesis of chondroitin sulfate present in the connective tissue ground substance and in the collagen Previous work has shown that cortisone inhibits and 17 ethyl 19 nortestosterone (Nilevar®) stimulates production of certain mucopolysaccharides that are essential in collagen fibrillogenesis and that specifically incorporate labeled sulfate Earlier work has also shown that Nilevar® but not testosterone propionate stimulated radiosulfur uptake in fractured rat humeri

METHOD —A closed fracture of the right humerus was produced in Wistar rats One group received 3 12 mg dihydrotachysterol in divided doses a second group received the same and also 50 mg Nilevar® in divided doses and a third group received no therapy After 3 weeks of treatment 100 μc radiosulfur was injected intraperitoneally The rats were killed 24 hours later Uptake of S was recorded as the ratio of counts per minute over the fractured bone and over the intact bone (F/I)

There was significant decrease in the F/I ratio in rats treated with dihydrotachysterol as compared with the untreated controls Simultaneous treatment with dihydrotachysterol and Nilevar® offset the catabolic effect of dihydrotachysterol significantly The inhibitory effect of dihydrotachysterol on tissue repair was comparable to the action of cortisone In other experiments the author found that the simultaneous treatment of animals with Nilevar and with

(9) [illegible] 1958

However most of these corpora lutea of pregnancy were associated with pathologic conditions Neither progesterone nor the Δ^4 3 ketopregnene 20 ol fraction could be found in uterine muscle or mucosa within the limits of the method used A compound was found in placental blood which was probably identical with Δ^4 3 ketopregnene 20 ol

New Compounds with Progestational Activity Review Demethylation at the 19 position of ethinyl testosterone increases in its progestational activity Four derived compounds the 19 nortestosterones are discussed by Fillmore Buckner and Walter Herrmann [8] The compounds are 17α methyl 19 nortestosterone (Neosteron) 17α ethyl 19 nortestosterone (Nilevar®) 17α ethinyl 19 nortestosterone (Norlutin) and 17α ethinyl 5(10) estren 17β ol 3 one (Enovid)

All 4 compounds given orally have greater progestational activity than oral progesterone and ethinyl testosterone in estrogen primed rabbits There is decreased activity with parenteral administration in some instances to level less than that of progesterone In humans all are more effective orally than progesterone Neosteron being 150 times as potent Withdrawal bleeding occurs with all 4 drugs in estrogen primed women but is difficult to evaluate since 3 of the compounds are known to be contaminated with estrogen

Neosteron and Nilevar® show androgenic activity which in humans is somewhat less than the activity of testosterone Despite their poor androgenic activity however all 4 drugs exhibit profound anabolic and myotrophic effects in animals and less so in humans

The compounds have multiple actions in preventing conception including inhibition of ovulation (in humans and animals) possible direct effects on the ovary and perhaps some damaging effect on the zygote

All have some inherent estrogenic activity in addition to the estrogen contamination In animals the compounds exhibit gonadotrophin inhibiting activity and this appears to a lesser extent in humans

At present the compounds are probably more important from the standpoint of their chemical structure and the possibility that their small variations from the activity of pro-

(8) Y 1 J P 1 & Med. 30 446-453 J 1958

)athic osteoporosis In contrast with the 2 patients with)crine osteoporosis he showed no significant nitrogen alcium retention and body weight decreased However er continuous norTPP treatment he became completely nptomatic clinically Several studies on the semen dur prolonged norTPP therapy revealed no change in quan or quality of the sperm or in the Leydig cell function he effect of norTPP was studied in 7 patients with mop)le metastasizing breast cancer 5 had bone metastases average weekly dose of norTPP was 50 100 mg Objec remission occurred in 4 In 2 complete relief from pain rease in phosphatase values and weight gain occurred hin a short time Combination of norTPP and x ray rapy produced the best therapeutic results None of the ıents showed signs of virilism The chances for hypercal na are much less with norTPP than with testosterone)ne of the authors patients who al o had kidney insuf ency the previously increased blood calcium level de ased under norTPP medication with normalization of nonprotein nitrogen value indicating a renotropic effect ding to increased tubular reabsorption

Antiandrogenic Activity of Synthetic Phenanthrene was died by Lowell O Randall and Joseph J Selitto (Nutley J) This compound 2 acetyl 7 oxo 1 2 3 4 4a 4b 5 6 7 9 10a dodecahydrophenanthrene (Ro 2 2739) has a super al resemblance to progesterone (Fig 75) which also in uts the androgenic and myotropic activity of testo ter e

Rats were castrated and 0 15 mg testosterone propionate sesame oil was injected ubcutaneou ly daily for 7 days) 2 7239 dissolved in se ame oil was injected subcutane sly in doses of 0 15 0 3 0 6 and 1 2 mg into the rats re ving testosterone Thus the ratio of androgen to antian ogen in the variou group was 1 0 1 1 1 2 1 4 and 1 8 group of controls received Ro 2 7239 alone in a dose of 1 2 g another group received only saline The rats were killed hour after the last d se and the weights of the eminal sicles prostate and levator ani muscles were compared ith similar weights in rats receiving only testosterone Es ogenic activity a measured by injecting Ro 2 7239 alone

cortisone resulted in an F/I ratio which was close to normal

The data confirm Selye's report that dihydrotachysterol and corticotrophin are catabolic as far as bone and cartilage metabolism are concerned and also his contention that some androgenic steroids offset the catabolic action of dihydrotachysterol. Clinical application of Nilevar® in preventing the dihydrotachysterol intoxication syndrome remains for further exploration

► [The compound 17α ethyl 19 nortestosterone has been reported to exert a specific effect on calcium metabolism. Plum and Dunning found it more effective that testosterone propionate in producing calcium retention in patients with hypercalciuria subsequent to acute poliomyelitis.—Ed.]

Clinical Experiences with 19 Nortestosterone Phenylpropionate (norTPP) are presented by H. Nowakowski and J. Paradi[1] (Hamburg). In animal experiments norTPP showed mainly metabolic and only minimal androgenic effect. It has been claimed that its progestational effect in the usual doses of 50-100 mg/week is negligible in human beings. The authors investigated its metabolic and androgenic effect in various diseases.

The effect of a single injection of 100 mg norTPP on nitrogen and calcium balance was studied in a woman aged 37 with Cushing's syndrome due to an adrenal tumor and severe osteoporosis of the entire spine. The balance studies began 8 weeks after adrenalectomy. After the injection she showed nitrogen retention which lasted up to 18 days and reached a maximum of 7 Gm. nitrogen during a 3 day period. The previously negative calcium balance became positive and the calcium retention increased steadily reaching 327 mg. during the last study period.

Nitrogen and calcium balance studies were made in a woman aged 28 with early eunuchoidism. At age 6 a craniopharyngioma had been removed which led to absence of gonadotrophin production. The spine showed severe osteoporosis. A single injection of 125 mg norTPP caused considerable nitrogen retention and weight gain of 1.7 kg within 18 days. Calcium retention was also definite. The effect of the single injection lasted for at least 15 days.

Similar nitrogen and calcium balance studies were done after a single norTPP injection in a man aged 34 with

(1) Deutsch med Wschr 83 1411-1414 (Aug) 1958

ularly induced limited masculinization Allopregnan 21 ol 3 20 dione acetate in ethanol or isopropanol reduced the percentage of eggs hatching and tended to be differentially lethal to female embryos Use of 2 methyl 3 ethyl 4 (p aminyl) Δ^3 cyclohexene 1 carboxylic acid in relatively low dose showed it was partially effective in inducing feminization Two 19 nor steroids had no androgenic or estrogenic effects a third 17 ethinyl estra 3 5 diene 3 7 diol diacetate at a high dose was lethal to all embryos A limited percentage of masculinization was induced by 17 methyl testosterone *progesterone and* Δ^5 *pregnenolone The corticosteroids except for 1 dehydrocortisol at low dose were lethal to all* embryos in the doses tested

A number of the feminized male chicks returned to normal male appearance with spermatogenesis by age 16 weeks Right orchiectomy did not prevent return to male appearance The other testis was sterile or had limited spermatogenesis Right gonadectomized birds fed on a regular diet plus diethylstilbestrol maintained the appearance and behavior of females but the left gonad was sterile and could not be stimulated by mammalian gonadotrophin administration

Estrogens appear to act directly on the mullerian duct rudiments The effects appear to be long term as the rudiments develop several days after absorption of the estrogens Masculinization of the female has not been accomplished as easily or to the same extent

Masculinization of Female Fetus Associated with Administration of *Oral* and Intramuscular *Progestins* during Gestation Nonadrenal Female Pseudohermaphroditism There are few reports of female pseudohermaphroditism not associated with congenital adrenal hyperplasia Lawson Wilkins Howard W Jones Jr Gerald H Holman and Robert S Stempfel Jr[4] (Johns Hopkins Univ) report 17 case of females born with partial masculinization of the external genitalia (enlarged phallus with or without varying degrees of fusion of the labioscrotal folds) and add to the c 4 *similar cases from the literature* Diagnosis was established by finding female chromatin patterns low excretion of 17 ketosteroids and absence of progressive virilization Explor

(4) J Cl E d 1 18 559 85 J 1958

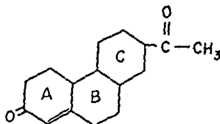


Fig 75 (C rt y of Randall L O d Sel tto J J J Cl E doc n l 62 693 695 May 1958)

and combined with estradiol benzoate into weanling female rats daily for 7 days at the end of which time the uterus weights were compared

In the 1 1 ratio of testosterone and Ro 2 7239 the seminal vesicle hypertrophy was inhibited 46% the prostate hyper trophy was inhibited 26% and levator ani growth was in hibited 18% Increasing doses of the inhibitor had greater antagonistic powers and the degree of inhibition was lin early related to the log dose indicating a competitive an tagonism between Ro 2 7239 and testosterone

Effects of Various Estrogens and Steroid Substances on Sex Differentiation in Fowl are documented by Gregory Pincus and Thomas F Hopkins[3] (Worcester Found for Ex perimental Biology Shrewsbury Mass) who used Seltzer method for medication of intact fertile chicken eggs The pointed end of the egg is dipped in a solution of a steroid for 5 20 seconds and then returned to the hatchery Solutions of diethylstilbestrol in ethanol and isopropanol were succes ful in producing feminization of as many as 98 4% of genetic males (gender being identified by a sex linked head spot) The percentage of hatched genetic males showing feminiza tion at hatching increased generally with increasing con centrations of diethylstilbestrol in the dipping solutions and to a point with increased immersion times Maximal mor phologic reversions were observed in isopropanol solutions of diethylstilbestrol

Ethinyl estradiol in ethanol induced significant percent ages of feminization whereas testosterone in ethanol irreg

(3) E doc i logy 6 11 118 F b y 1958

studied would probably never have been born without their use After early and accurate diagno is corrective proce dures can be instituted as necessary Retrospectively it ap pears possible that in some instances this condition could be avoided by using smaller doses of oral proge tin and de ferring if po sible their administration until after the 10th week of pregnancy

Relaxin Clinical Review i presented by Richard N Sands (Women s Ho p New York) Although relaxin i elaborated by the ovaries during pregnancy and has been shown to affect certain aspects of reproduction it al seems to act in conditions which are unrelated to pregnancy This is probably due to the fact that the action of the hor mone is exerted on one tissue in common—connective ti sue Relaxin reverses the aging processes in connective ti sue and from this fundamental physiologic activity all the actions of relaxin stem

Relaxin is being used with good results in the treatment of scleroderma and many conditions associated with fibro i such as hepatobiliary fibrosis postirradiation fibro i lymph edema corneal opacity keloidosis and fibrous tis ue con tractures around joints in muscular dystrophy Similarly encouraging results have been reported in the treatment of dysmenorrhea and peripheral va cular diseases

Too many responsible investigators have reported that relaxin is effective in arresting premature labor for this to be a chance observation However it is likely that the effec tiveness is found in premature labor arising from exce ive irritability of the uterus probably caused by an imbalance of estrin and progesterone It is unlikely that relaxin would have any effect in premature labor arising from fetal death or placental lesions and in abruptio placentae or accidental hemorrhage its use would actually be contraindicated

Many obstetricians feel that arresting labor during preg nancy and po sibly facilitating and accelerating it at term— two observed actions of relaxin—are incompatible How ever it is possible that the ancillary hormone balance the concentration of estrogens and proge terone may be re sponsible for this

(5) C 1 M A J 8 935 940 J 15 19 8

atory laparotomy revealed normal ovaries and a normal female genital tract although in some patients the vagina and urethra opened into a common urogenital sinus In 15 of these cases the mother had been treated with an oral progestin 17 ethinyltestosterone for threatened or habitual abortion Two mothers had received only intramuscular injection of progesterone One had been given intramuscular injections of progesterone besides oral methyltestosterone Three mothers had received intramuscular progesterone plus oral progestin and 2 had received weekly injections of 17α hydroxyprogesterone caproate The dosage of 17 ethinyltestosterone varied from 30 to 200 mg/day but in general the mothers whose infants were most masculinized had received the largest dose Only 3 mothers had no history of steroid therapy during pregnancy In 2 of these 3 however there was a definite history of spontaneous mild hirsutism and acne in previous pregnancies or in the pregnancy concerned

Diagnosis as early in infancy as possible is of the utmost importance and rests on the features mentioned When diagnosis is made in infancy the patients should be reared as females irrespective of the structure of the external genitalia The child will develop and mature as a normal female and menstruation will occur without hormone therapy Plastic repair of the external genitalia can be carried out as indicated In 1 case the child had been reared as a male until age 12 years and it was elected not to change his assigned sex accordingly panhysterectomy ovariectomy and mastectomy were performed

It seems probable that the testosterone or other androgen crossed the placental barrier and caused masculinization of the external genitalia of the fetus in instances in which the mother was so treated The mothers had shown mild evidence of virilization In the 3 cases in which the mother received no steroids during pregnancy the cause of fetal masculinization is obscure Two of the mothers had evidence suggestive of increased androgen secretion during pregnancy

That oral or intramuscular progestins may occasionally cause partial masculinization of the female fetus does not indicate that these steroids should be abandoned in the treatment of habitual or threatened abortion Most of the patient

gated X ray dosage was 3 000 1 500 1 000 and 500 r After 3 000 r the ovaries became markedly atrophic ova and follicles were absent and only atrophic remnants of corpora lutea and solitary interstitial cells were noted

The ovaries of the irradiated animals no longer had an inhibiting influence on secretion of gonadotrophins This was borne out by the findings in the nonirradiated animal the ovary of the latter was hyperplastic because of marked follicular hyperplasia in some cases the follicles were markedly dilated and quite often cystic large corpora lutea were present and the vaginal epithelium showed mucification which is a sign of intensified secretion of both estrogens and progesterone

Conditions in the animals treated with 1 500 r were slightly different The ova and primordial follicles were completely destroyed but more or less intact atresic follicles and corpora lutea were present The histologic appearance of the interstitial cells was normal The endocrine function of the ovaries was retained This was demonstrated by the findings in the nonirradiated parabionts the ovaries did not increase in weight and the follicles were histologically normal in all but 2 in which there was some suggestion of follicular hyperplasia

Except in 1 animal conditions in the group treated with 1 000 r were practically identical with those in the group given 1 500 r In the group which received 500 r damage to the ovary was not sufficiently severe to destroy primordial follicles containing ova or growing follicles It is therefore not possible to draw any conclusion from the findings in this group as to the possible influence of interstitial cells on endocrine function of the hypophysis

The findings substantiate the view that the interstitial cells secrete estrogens No information was obtained as to how long they maintain possible endocrine activity after destruction of the ova and follicles but the findings suggest that it continues only for a limited period after degeneration of the granulosa cells

► [While small doses of x radiation often produce transient or even permanent amenorrhea total ablation of ovarian endocrine function may be difficult to achieve One difficulty is that criteria for cessation of such function are hard to come by I am frequently asked how much x ray is necessary to produce roentgen castration particularly in the treatment of a l

However despite the reported alteration of uterine contractions of early labor in primigravidas particularly the relaxin treated patient seems to have less pain is more cooperative requires less sedation and bears labor with greater equanimity so that relaxin could justifiably be described as a uterine anodyne The combination of cervical softening and perineal relaxation induced by relaxin plus its anodyne effect should logically result in shortening of labor

The softening effect of relaxin on fibrosed tissue is still to be investigated in the treatment of sterility due to stenosed cervix or to old pelvic inflammatory disease When pregnancy finally results in patients so affected the incidence of cervical dystocia is high and relaxin is indicated to facilitate the problems associated with this state The effect of relaxin on cervical problems associated with breech delivery is another indication which should be investigated

In view of the animal origin and protein like nature of the hormone the possibility of anaphylaxis must be kept in mind However generally toxicity is not an important feature of relaxin therapy

Experimental Evidence for Existence of Uterine Hormone Hysterectomy in rabbits causes degeneration of the ovarian follicular structure and development of the interstitial body B Tenney F Parker Jr and S L Robbins[6] (Boston City Hosp) report that these ovarian changes were prevented in the rabbit with biweekly injections of an aqueous extract of human uterus for 12 weeks after hysterectomy

From this study and other evidence the authors conclude that the uterus appears to have an endocrine function

► [These authors have made a number of interesting studies which contribute substance to the clinical impression that ovarian failure is a common consequence to hysterectomy This has usually been attributed to interruption of ovarian blood supply but these studies suggest a humoral relationship —Ed]

Influence of X radiation on Hormonal Function of Ovary was studied by Axel Westman[7] (Karolinska Hosp Stockholm) A nonirradiated laboratory animal and an irradiated animal were united in parabiosis and the anatomic and functional changes in the ovaries of both animals were investi

(6) A J Ot t & C 5 65 ff M h 1958
(7) A ta e doc i I 9 134 346 1958

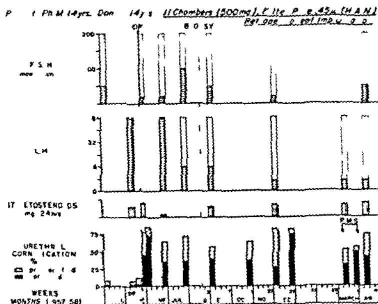


Fig 6 (Courtesy of S... S H and C ... H ... Am J Obst & G... 6 113 114 ... mber 1958)

cally conditioned toward the male and only secondarily modified in utero toward the female and are incapable of responding readily to estrogenic stimulation

Endocrine homotransplants in humans may be protected from destruction by implantation in Millipore filter chambers and production of estrogenic steroids—although clinically ineffective—has been demonstrated by laboratory indexes

Clinical Pathologic Conference Philadelphia General Hospital Norman Schneeberg[9] discussed the case of a young women who died of estrogen withdrawal hemorrhage

Woman 20 gravida 0 was admitted with a hemoglobin level of 3 6 Gm after a history of metrorrhagia for about 1 month She had been followed in the Endocrine Clinic for 2½ years initially having been referred for amenorrhea Daily estrogen and progesterone every 4 weeks was started after 2 weeks of therapy the patient began to bleed per vaginam almost every month averaging 3 4 days per period Her previously pubescent breasts continued to develop normally Axillary

(9) ... P ... & D ... T ... 9 641 649 ... 1 1958

vanced breast cancer in young women The best information I have found i that given by D L Gordon and A Segaloff in Breast Cancer (St Louis C V Mosby Company 1958 [p 187]) They recommend 1 200 r or more (tis ue dose) over a period of 2 weeks or longer —Ed]

Ovarian Homografts in the Primate Experience with Millipore Filter Chambers Somers H Sturgis and Hector Ca tellanos[8] (Boston) with the technical assistance of John Rahilly studied results of transplantation of normal ovaries within Millipore filter chambers in 3 patients of chromatin negative (male) genetic type In these chambers the membranes exclude all circulating cellular elements yet the pores are large enough to allow diffusion of proteins and electrolytes sufficient to nourish the enclosed tis ue Earlier work by Algire and others showed that nonvascularized homotransplants can survive without destruction for indefinite periods when so enclosed The present authors attempted to maintain survival and achieve physiologic function in the transplanted tissue as well

Patient aged 14 4 ft 3 in tall had moderate webbing of the neck no econdary sex characteri tics and high gonadotrophin level Pelvic laparotomy revealed thin white linear conglomerate of fibrous tissue only under two fallopian structures that united at a rudimentary cervix There wa no uterus The patient s cour e i hown in Figure 76 Eleven chambers with 500 mg ovarian tissue from a donor with polycystic ovaries were implanted The increa e in cornification count and decrea e in FSH directly after operation may be attributed to the amount of estrogen in the grafted tis ue Seven months later even though almo t full cornification was present and FSH and LH levels were well below preoperative values there were no changes in the patient s clinical appearance A 3 weeks cour e of injections of pregnant mare s serum induced no clinical change The FSH level is once again at the preoperative level

In thi and the 2 other patients suggestive evidence of changes in gonadotrophin levels and urethral cytology were noted but have not been sustained and subjective evidence of clinical improvement due to estrogen is meager or lacking This i in contrast with experience with successful functioning of ovarian auto and homotransplants as nonvascularized grafts in rats and monkeys The reasons for failure are not definite at this time Insufficient tissue may have been tran planted Of po sibly more significance however is the fact that the sex chromatin pattern of these 3 patients was of the male type It may be that the target organs are geneti

(8) Am J Ob t & Gynec 6 1132 114 November 1958

s do a_e schedule revealed that 1 25 m_ Premarin* dequately reduced the cholesterol pho pholipid and pha lipoprotein cholesterol ratios in women whose were initially below the group mean In women with nitially above the group mean this dosage failed to : a comparable level Increase in do a_e to 2 5 mg e ulted in satisfactory lowering of the cholesterol olipid ratio although the beta alpha lipoprotein erol ratio remained somewhat elevated

plications of estrogen therapy were noted but were nous They included breast tenderness recurrence of ne and nocturnal leg muscle cramps Breast tender as temporary but migraine or leg cramps when suf ly evere made necessary the cessation or decrease of en do a_e

ience of Androgens Estrogens and Related Steroids rum Lipids and Lipoproteins Observations in Hypo al and Normal Human Subjects Robert H Furman lmer Howard Leonard V Norcia and C Corinne (Univ of Oklahoma) studied serum from 60 hu ubjects by ultracentrifugation methods It was found estrogens promptly and consistently increased high y $-S_{1\ 1}$ 0 12 (alpha) lipoprotein concentrations eas androgens promptly lowered them The concentra f lower density$-S_{1\ 1}$ 25-40 (beta) or $-S_{1\ 1}$ 25 70 lipo ins characteristically did not change or changed in a tion opposite to that of the high density lipoproteins gonadal steroids were given

sponse of the chemically determined serum cholesterol phospholipid concentrations may be predicted on the of the lipoprotein changes induced by gonadal ste in individual subjects When the concentrations of and lower density lipoprotein fractions changed in op e directions serum cholesterol and phospholipid levels ed little or no change When lower density lipoprotein entrations failed to change after gonadal steroid exhi n then serum cholesterol and phospholipid levels ged in the same direction as that of the high density roteins Serum phospholipids tended to vary with the

Am J Med 24 80 7 J u y 1958

and pubic hair growth had started at age 9 or 10 There was webbing of the neck The clitoris was slightly enlarged The external genitalia were otherwise normal The patient was 4 ft 11 in tall

Shortly before admission the patient had bled for about a month with passage of clots This was followed by a week of amenorrhea Subsequently bleeding again developed per vaginam and she passed clots The mother stated that the patient had headaches and fainting spells for 2 months before admission The patient died within 4½ hours after admission despite blood and intravenous fluid therapy

The diagnosis of gonadal dysgenesis was confirmed at autopsy The ovaries were not present and no ovarian vestiges were recognized The endometrium was thickened and desquamating but no product of conception was identified Death was due to massive pulmonary edema secondary to anemia There was no genital lesion to which to attribute the bleeding other than the endometrial hyperplasia

In summary this is a case of death from hemorrhage consequent to the cyclic estrogen withdrawal

Estrogen Replacement Therapy in Women with Coronary Atherosclerosis Roger W Robinson William D Cohen and Norio Higano[1] (Mem l Hosp Worcester Mass) report significant differences in the serum lipid patterns between normal young women and postmenopausal women In postmenopausal women the elevation of serum total cholesterol is greater than that of the serum phospholipids resulting in an increased cholesterol phospholipid ratio The ratio of cholesterol in the beta lipoprotein fraction to that in the alpha fraction is also significantly increased To determine whether specific serum lipid abnormalities are characteristic of women with coronary heart disease the data on 58 patients were compared with those of 113 normal postmenopausal women The only significant difference was an increased beta alpha lipoprotein cholesterol ratio in the coronary group

To study the effects of estrogen administration on serum lipids previously hysterectomized women with coronary heart disease were treated with a high dosage schedule of 5 or 10 mg Premarin® daily for 2 to 31 months There was a dramatic serum lipid response as early as 1 month with reduction of the cholesterol phospholipid and beta alpha lipoprotein cholesterol ratios to levels comparable to those of normal young women within 3 months

(1) A n I t M d 48 95 101 J y 1958

The presence of a well developed fern pattern at midcycle indicates good estrogen activity and a healthy cervical canal which should be receptive to sperm penetration

Atypical fern must be distinguished from true fern The appearance of fern in early pregnancy might indicate the need for substitutional progesterone therapy in patient who

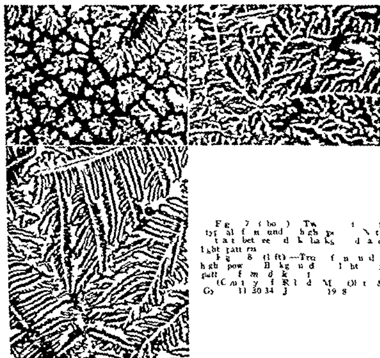


Fig 7 (abo) Tw t 3 typ al f n und h gh p N t t a t bet ee d k ba ks d a d l ght patt rn
Fig 8 (l ft)—Tru f n u d h gh pow B kg u d l ht l patt f m d k t
(C m t y f R l d M Ol t & Gy 11 30 34 J 19 8

are habitual aborters The finding of true fern eliminates the diagnosis of pregnancy after a missed period The cause and significance of atypical fern are uncertain It can be differentiated from true fern by changing the focus of the microscope from low to high power as the focus is changed on atypical fern the entire background remains black and the stem with its offshoots are light (Fig 77) In true fern the main stem as well as the off hoots appear to become dark whereas the background remains relatively clear (Fig 78)

high density lipoprotein concentrations more than did the serum cholesterol presumably because of the relatively high phospholipid cholesterol ratio of the $-S_f$ 0-12 lipoproteins

Changes induced in serum lipoproteins by gonadal steroids tended to persist for 1 or more weeks after therapy was dis continued and after nitrogen balance had returned to the control state No wearing off phenomena were observed The responses of the lipoproteins were not conditioned by urinary gonadotrophin or 17 ketosteroid excretion and may be elicited in hypothyroidism and panhypopituitarism

The changes induced in the serum lipoproteins of human subjects by gonadal steroid administration suggest that the relative immunity of women to coronary atherosclerosis may be attributable to relatively large concentrations of high density lipoproteins or to relatively high values for high density/lower density lipoprotein ratios The data also in dicate the necessity for study of the entire serum lipopro tein spectrum if the physiologic or etiologic importance of these lipoproteins in health and disease is to be fully evaluated

► [In a subsequent paper (Clin Res 6 262 1958) the authors showed that the characteristic effect of androgens on lipids may be abolished by reducing the protein content of the diet If one assumes that a high beta alpha lipoprotein ratio does predispose to atherosclerosis the only thera peutic suggestions for the fragile male heretofore have been castration feminization or starvation Perhaps some less drastic approach will evolve from this interesting demonstration —Ed]

Fern Test Critical Analysis is presented by Maxwell Roland[3] (Albert Einstein College of Medicine) who in 1952 suggested the fern phenomenon as a test for ovulation es trogen activity and early pregnancy as well as for progno stication of impending abortion The fern pattern is thought to be due to sodium chloride and a mucin like substance The protein concentration is critical Estrogen is believed to be responsible for the arborization of cervical mucus through its control of sodium chloride metabolism A fern pattern is no longer present when the progesterone reaches a high level on about the 22d day of the normal cycle

The presence of blood or cervical infection will inhibit true fern formation Although the test is of use in predicting the fact of ovulation it is not of value in pinpointing the day

(3) Obst & Gyn 11 30-34 January 1958

cles that have been supplying estrogen Nevertheless tem porary but sudden reduction in the estrogen level results with concomitant increase in gonadotrophin

Stein Leventhal Syndrome Review and Case Reports presented by Rufus P Ellett Jr and Donald D Barnes (Roanoke Mem l Hosp) call attention to the diagnosis pathogenesis and treatment of bilateral polycystic ovaries

Menstrual irregularities may be observed after an interval of normal cycles or from menarche Irregularity is often fol lowed by hypermenorrhea which may be severe oligomen orrhea and finally by periods of amenorrhea lasting from 8 weeks to 9 years Sterility is usually primary but may de velop after one pregnancy Hirsutism obesity and a male es cutcheon are fairly common Underdevelopment of the breasts is less frequent Acne may appear Hypoplasia of the uterus is often found with occasional hypertrophy of the clitoris

Bilateral polycystic ovaries enlarged 2-4 times must be observed for an absolute diagnosis of Stein Leventhal syn drome Palpation may be hindered by obesity or a mascu linized abdominal musculature Pneumoroentgenography and culdoscopy have proved useful in diagnosis

The ovarian surface is smooth and usually glistening white Larger cysts may be visible through the capsule but the cy ts are usually *not elevated* Since ovulation is rare the ovary does not show wrinkling fre ly ruptured follicles or corpora lutea A cut section shows a thickened tunica albu ginea a dense stroma and multiple cysts ju t beneath the capsule Many follicles are seen in all stages of development the cysts lined by single layers of granulosa cells or theca cells in more advanced cases The graafian follicles appear fairly normal

Its etiology is obscure but the disease is not congenital in flammatory or degenerative The thickened tunica albuginea and restoration of function after its removal suggest a me chanical barrier to the ripening follicles However the si multaneous bilateral enlargement suggests an extraovarian influence Several hypotheses have been advanced

Wedge resection appears to be the most satisfactory treat

(5) Am J Ob t & Gyne 4 1 01 1 0 Dec mbe 1957

Stein Leventhal Syndrome

Polycystic Ovarian Disease (Stein Leventhal Syndrome) Etiology and Rationale for Surgical Treatment were studied by Tommy N Evans and Gardner M Riley[4] (Univ of Michigan) Of 25 patients in whom bilateral wedge resection of the ovaries was carried out after diagnosis of the Stein Leventhal syndrome in 19 ovulatory cycles developed postoperatively Since operation 16 have had a total of 28 pregnancies In 6 patients poor or no therapeutic response was obtained after operation Laboratory endocrine evaluation showed significant differences between the patients who responded after operation and those who did not A good result was achieved only in those who preoperatively were found to have consistently normal estrogen and follicle stimulating hormone (FSH) excretion rates The distinctions between these two groups of patients are such that it is felt that preoperative laboratory endocrine evaluation will permit a high degree of accuracy in predicting the response to ovarian wedge resections Normal FSH and estrogen levels are essential

Three patients who conceived after operation had ovaries of normal size and 1 of these showed no appreciable cystic change The most consistent histologic change was follicular hyperplasia Although theca cell hyperplasia is conspicuous a granulosa layer can usually be found with mitotic activity often noted in both layers

On the basis of clinical conditions associated with polycystic ovaries and experimental methods for their production it is believed that multiple follicle cysts in human beings probably develop because of continued exposure of the ovaries to FSH with insufficient luteinizing hormone to induce ovulation and luteinization Any clinical condition or period of life that is associated with a disturbance of or variation in the normal pituitary ovarian relationship appears to predispose to the development of polycystic ovaries This theory also provides a rationale for use of ovarian wedge resections in its treatment This operation results in excision of many but not all of the cystic and atresic folli

(4) Obst & Gynec 12 168-178 August, 1958

was equally dramatic despite absence of wedge resection suggesting that favorable results in the first case were not due to operation alone The third patient showed mixed adrenocortical hyperfunction Fall of 17 ketosteroids to normal with large amounts of prednisone indicated hyperplasia rather than tumor as was confirmed by adrenal exploration The Stein Leventhal like ovaries suggested an etiologic relation because hirsutism (adrenal) was progressive for 4 years whereas ovarian changes obviously were early and slight This reasoning applied equally to 3 other patients In the seventh patient adrenal hyperfunction was due to a tumor presumably not under endocrine control and therefore it was the primary lesion ovarian changes probably were secondary

Wedge resection of the ovaries possibly affects the menstrual status primarily whereas adrenal suppressive therapy such as prednisone acts more physiologically improving ovarian and adrenocortical functions The pathologic sequence may be that a primary adrenocortical metabolic defect leads to low serum corticoids increased pituitary corticotrophin production and consequent increase in adrenocortical androgen which produces ovarian follicular cysts These elaborate estrogen which in turn causes further adrenocortical hyperfunction via the pituitary gland Beneficial effects of wedge resection probably are due to removal of estrogen producing tissue and prednisone acts by ameliorating the primary adrenal metabolic defect

Ovarian Tumors

Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women Since fetal and maternal tissues require high amounts of folic acid for their normal metabolism the therapeutic potential of the folic acid antagonist 4 amino N[10] methylpteroylglutamic acid (methotrexate) in treatment of choriocarcinoma and related trophoblastic tumors was studied in 27 women by Roy Hertz Delbert M Bergenstal Mortimer B Lipsett Edward B Price and Theodore F Hilbish (Nat'l Inst of Health) Remission of 2 29 months were induced in all but 1 patient who had received more than one course of therapy

(7) J A M A 168 845 854 Oct 18 '59

ment The remaining follicle cysts are perforated and the defect is closed with fine catgut Wedge resection with extroversion and decortication have also been advocated Dilatation and curettage have been recommended for all patients with menometrorrhagia associated with this syndrome to rule out endometrial carcinoma First patients underwent wedge resection which was followed by resumption of normal menstruation Two of these had normal pregnancies and deliveries and a third is pregnant at the time of this report Similar results reported by others in more extensive studies show that the symptoms except hirsutism are relieved after wedge resection

Stein Leventhal Ovary Manifestation of Hyperadrenocorticism William H Perloff Bertram J Channick Harry E Hadd and John H Nodine[6] (Temple Univ) in a previous study on patients with idiopathic hirsutism in which urinary total neutral 17 ketosteroids were separated into $C_{19}O$ (strong androgen precursors) and $C_{19}O_3$ (weak androgens) fractions found the ratio of $C_{19}O$ to $C_{19}O_3$ substances to be higher than normal and identical with that in the Stein Leventhal syndrome as was the response of these fractions to prednisone administration In another study in which urine samples were subjected to sequential hydrolysis to determine how urinary 17 ketosteroids are conjugated before renal excretion a similarity between these two conditions was noted These experiences led the authors to question whether Stein Leventhal ovaries and adrenocortical hyperplasia might be manifestations of the same fundamental metabolic aberration or whether ovarian dysfunction might be the natural development of adrenocortical hyperfunction

Clinical and laboratory data on 7 patients suggested that ovarian changes are secondary to virilizing adrenocortical hyperfunction Ovaries of the first patient were of the Stein Leventhal type wedge resection improved the menstrual status for 10 months Temporary slowing of facial hair growth seemed to be correlated with transient reduction of 17 ketosteroids Prednisone therapy yielded even more favorable results in hirsutism menstrual regularity and levels of urinary 17 ketosteroids Improvement of the second patient

(6) Fe t l & Ste I 9 4 55 M y J 1958

was noted all hormonal radiologic and physical evidence of the tumor remained in abeyance for 8 29 months (Fig 79) Partial remission was obtained in 7 and transient remission in 10 Six patients died after initial transient response

Treatment involved a substantial hazard Side effects were often severe and not always reversible but because of the striking nature of the results in some patients the morbidity and mortality must be accepted as hazards of the treatment in its present form

Ovarian Estrogenic Tumors and Diffuse Estrogenic Thecomatosis in Postmenopausal Colporrhagia Importance of Benign Endometrial *Mitosis* *Robert Fienberg*[8] *(Harvard Med School)* reports 6 cases selected from 140 Presence of active estrogen secretion was demonstrated by the finding of benign endometrial mitoses with hyperplasia In general the endometria showed elongated glands occasionally *branched* and sometimes *cystic* *The noncystic glands were* lined by tall columnar cells with abundant cytoplasm and plump nuclei whereas the cystic glands were usually lined by flat to low cuboidal epithelium with scanty cytoplasm and small hyperchromatic nuclei Pseudostratification was also *noted* The stroma was often cellular but in a few regions was fibrotic and hypocellular and here the cystic dilatation of the glands was most prominent Most important of all was the presence of mitotic figures in both glands and stroma In 2 patients ovarian thecomas were noted and 3 showed *mixed granulosa and theca cell tumors at laparotomy* A sixth showed estrogenic thecomatosis No palpable adnexal masses were felt in 4 of the women

Any colporrhagic woman with postmenopausal amenorrhea for over 3 years and hyperplasia of the endometrium with *mitotic figures should have an exploratory* laparotomy whether or not a palpable adnexal mass is present provided no exogenous estrogen has been given Lesions of the fundus and cervix must be ruled out Endometrial hyperplasia without mitotic figures indicates that estrogenic activity has occurred but is not necessarily concurrent The only definite histologic indication of concurrent estrogen activity is the benign endometrial mitotic figure

(8) Am J Obst & Gynec 6 851 860 Oct 1958

Fig 9 [illegible] (J A M A 168 845 854 Oct 18 19[illegible])

The drug was given in 5 day courses at a daily dose of 10 30 mg usually administered intramuscularly but some times by continuous intravenous drip Therapeutic indexes included serial x rays physical findings reflecting pelvic cerebral and pulmonary involvement and frequent quan titative determination of urinary excretion of chorionic gonadotrophic hormone In 5 patients complete remission

bleeding Budding breasts were observed downy pubic hair and somewhat enlarged external genitalia Urinary estrogens were positive at 10 m u and FSH was negative at 3 3 m u /24 hours A vaginal cytologic smear showed 65% cornification At laparotomy the left ovary was shown to be replaced by a pearly white encapsulated slightly flattened tumor 6×5×3 cm which was easily removed The tumor showed a yellowish firm cortex with multiple small cystic cavities Microscopically the tumor was composed of granulosa and theca type cells with luteinization of both elements in many areas (Fig 80) This was thought to be a granulosa theca cell tumor with luteinization Postoperatively a bloody vaginal discharge was present for 2 3 days and 5 days after operation a vaginal smear showed reversion to an immature basal type of cell with only 5% cornification Eventually cornification disappeared and assays of urinary estrogens and FSH became negative

Case 2 supports the viewpoint that granulosa and theca cells are derived from ovarian stromal mesenchyme by differentiation and that both elements are capable of luteinization which is commonly demonstrated in the corpus luteum The author believes many so called granulosa cell tumors are mixed granulosa and theca cell tumors a view more acceptable in cases of tumors that show functional effects due to estrogen production as it is generally thought such hormones are elaborated by theca rather than granulosa cells

Granulosa Cell Tumor in Infant Aged 15 Months is reported by C T Gurson B R Gorbon D B Pars and Ö Bedir[1] (Istanbul)

Infant aged 15 months was hospitalized She weighed 3 250 Gm at birth and development was normal until age 6 months when she weighed 10 kg She became increasingly irritable At 7 months enlargement of the abdomen and development of pubic hair were noted Breast development began at 12 months and axillary hair appeared at 13 months She cut the first teeth at 6 months and walked at 9 months

At 15 months weight was 13 6 kg and height 88 cm The figure was rounded and the abdomen protruded Pubic hair was thicker than that in the axilla The labia were overdeveloped and the clitoris was comparable to that of an adolescent aged 16 Palpation showed a large hard abdominal mass the lower portion of which could be felt on the right by rectal examination The uterus was of average size X rays revealed a large homogeneous opaque mass displacing the colon and small intestine toward the left Intravenous pyelography showed normal kidneys The right ureter was ectatic and showed stasis Urinary 17 ketosteroids measured 5 mg total estrogen 720 µg and pregnanediol 0 9 mg

Clinical diagnosis of granulosa cell tumor of the right ovary was

(1) H l t s 3 t 1 12 548 552 N mber 1957

Precocious Pseudopuberty of Ovarian Origin with Report of Two Cases is presented by F J Tweedie[9] (Montreal)

CASE 1—Girl 7 had a 3 year history of breast development There were brown pigmentation of the nipples and limited growth of pubic hair X rays showed a skeletal age of 10 years Urinary estrogen assays were positive at 320 m u /24 hours Pituitary follicle stimulating hormone (FSH) was negative at 6 6 m u /24 hours 17 ketosteroids were 2 6 mg /24 hours A 3 cm cyst was found on the right ovary which microscopically was shown to be a theca lutein cyst

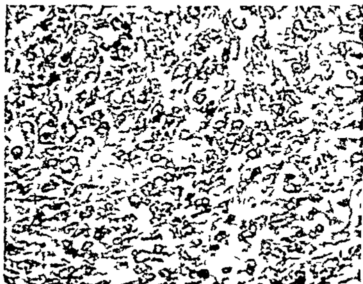


Fig 80—High power section of the wall showing luteinized cells of granulosa and theca type (Courtesy of Tweedie F J Am J Obst & Gynec 75 964 969 May 1958)

Its morphologic appearance was consistent with the functional effects observed The cyst fluid had an estrogen activity of 5 10 m u /cc

Although the rare association of sexual precocity with follicular ovarian cysts has been ascribed to constitutional precocious puberty evidence against this supposition includes (1) the static condition of this cyst for the few weeks before operation (2) absence of FSH (3) the complete reversion to normal immature status after removal of the cyst (4) the infantile appearance of the uninvolved ovary and (5) the demonstration of estrogen activity in the cystic fluid

CASE 2—Girl aged 20 months was admitted because of vaginal

(9) Am J Obst & Gyn 75 964 969 May 1958

Woman 26 nulliparous with history of amenorrhea and signs of masculinization was hospitalized She had had increasingly excessive growth of body and facial hair since age 18 and had shaved the face regularly for about 2 years Physical habitus was masculine A mustache and a small amount of chest hair were noted and distribution of pubic hair was masculine The clitoris was enlarged the vagina and cervix were normal and the uterus was anterior and of normal size No pelvic masses were palpated Urinary 17 ketosteroid excretion was elevated to 27 5 mg /24 hours Sections of epidermis showed the genetic sex to be female

On laparotomy the internal organs appeared grossly normal No abnormalities were found on palpation of the adrenal gland areas Gross pathologic examination of the ovary showed no abnormality but section across the midportion revealed a small firm yellow circumscribed nodule in the medullary and hilar regions

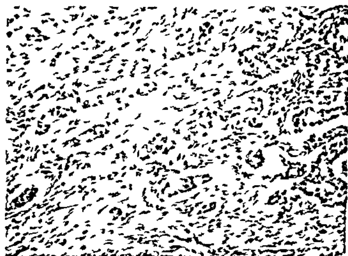
Under low magnification of the entire cross section two separate tumors were seen One located in the center of the ovary was made up of round or elongated masses of cells separated by the fibrous stroma of the tumor and ovary itself Under higher magnification these masses proved to be granulosa cell tumor (Fig 82) Masses of granulosa cells occupied sites in the ovarian cortex close to the surface suggesting invasion The other tumor was more clearly encapsulated and lay within the mesovarium next to the hilus It was comprised of large clear cells and smaller ones with denser eosinophilic cytoplasm (Fig 83) Both resembled the hilus cells found in the normal ovary the smaller cells more than the larger ones

Close study of the cortex disclosed two unusual features The first was presence of large polyhedral cells distributed at random which were similar to the hilus cells but which also resembled luteinized cortical stroma cells—the so-called thecosis of ovarian cortex There were areas where these cells merged with the granulosa cell tumor In this context it seemed reasonable to suppose that these polyhedral cells were luteinized stromal cells Other areas showed almost identical cells adjacent to clusters of undoubted hilus cells The second feature was presence of small foci of calcium scattered throughout Most seemed to be embedded in the cortex at random but some were surrounded by a layer of cells of the type which surround the primordial ovum suggesting that calcification had occurred in primordial follicles A few primordial follicles were intact in some of the section and an occasional ovum was seen

Histologically the granulosa cell tumor was typical and occupied a position quite apart from the other growth Similarly the hilus cell adenoma was circumscribed and made up of the characteristic cells These two features—anatomically separate masses and cytologically typical components—favored the decision that there were two neoplasms a granulosa and a hilus cell tumor

Follow up 2 years later showed partial regression of the signs of masculinity though there was still some growth of facial hair On several tests of urinary 17 ketosteroid excretion the average was 11 9 mg /24 hours

confirmed at operation The tumor 20×15×12 cm was soft smooth oval and regular Transverse section showed several round cysts of varying size Between these and around cavities were yellowish nodular regions of different sizes Hemorrhagic edematous and fibrous areas were dispersed among cystic and nodular foci Sections from different portions of the tumor showed regions of ovarian stroma rich in nuclei and presenting edema or lipoid cells in some places Rounded irregular mas e columns and in places reddish cytoplasm re embling tubular cells with narrow lumens were een in the ovarian stroma In some places these cells formed cystic structure contain



F g 81 (C t y of G sc C T r J H I t p d at t J 485 Novmbe 195)

ing mucous secretion and resembling primordial or graafian follicles (Fig 81) There were also areas of fibrous degeneration among the masses of cells in these regions Some epithelioid cells of the stroma had pyknotic nuclei as well as large dark nuclei Erythrocytic infiltrations and dilated vessels were also pre ent Some of the large cystic cavities were covered with a layer of endothelium

Urinary examination 24 hours after operation showed 17 keto teroids 0 82 mg total estrogen 125 μg and pregnanediol 1 2 mg

General behavior improved but no change was noted in symptoms of endocrine dysfunction at the time of the report

With the exception of a single case this is the youngest patient on record with a tumor of follicular cell

Hilus Cell and Granulosa Cell Tumors in Same Ovary are reported by Cary M Dougherty William Benbow Thompson Jr and Milton L McCall (New Orleans)

( ) Am J Ob t & C c 6 (53 (5 S pt be 1958

man 26 nulliparous with history of amenorrhea and signs of ... [illegible] was hospitalized. She had had increasingly excessive growth of body and facial hair since age 18 and had shaved the face ... [illegible] for about 2 years. Physical habitus was masculine. A ... and a small amount of chest hair were noted and distribution of the hair was masculine. The clitoris was enlarged, the vagina and ... were normal and the uterus was anterior and of normal size. No pelvic masses were palpated. Urinary 17 ketosteroid excretion was elevated to 27 5 mg./24 hours. Sections of epidermis showed the nuclear sex to be female.

At laparotomy the internal organs appeared grossly normal. No abnormalities were found on palpation of the adrenal gland area. ... pathologic examination of the ovary showed no abnormality ... section across the midportion revealed a small firm yellow circumscribed nodule in the medullary and hilar regions.

Under low magnification of the entire cross section two separate tumors were seen. One located in the center of the ovary was made up of round or elongated masses of cells separated by the ... [illegible] of the tumor and ovary itself. Under higher magnification these masses proved to be granulosa cell tumor (Fig 82). Masses of granulosa cells occupied sites in the ovarian cortex close to the ... suggesting invasion. The other tumor was more clearly encapsulated and lay within the mesovarium next to the hilus. It was ... composed of large clear cells and smaller ones with denser eosinophilic cytoplasm (Fig 83). Both resembled the hilus cells found in the normal ovary, the smaller cells more than the larger one.

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Histologically the granulosa cell tumor was typical and occupied a position quite apart from the other growth. Similarly the hilus cell adenoma was circumscribed and made up of the characteristic cells. These two features—anatomically separate masses and cytologically typical components—favored the decision that there were two neoplasms, a granulosa and a hilus cell tumor.

Follow up 2 years later showed partial regression of the signs of masculinity though there was still some growth of facial hair. On several tests of urinary 17 ketosteroid excretion the average was 11 0 mg./24 hours.

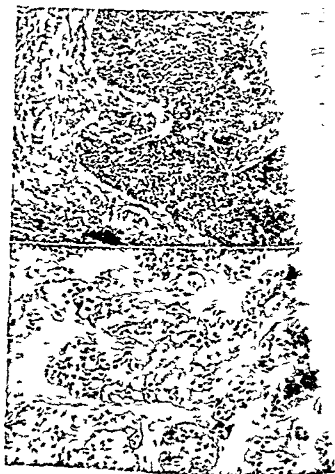


Fig 8 (top) — Typ l g l sa ll t m w th n v
Fig 83 (bot m) — H l ll a l ma n meso m
(C rt y f D gh rty C M t al Am J Ob t & Gynec. 6 6 365
t mbe 1958)

To determine the possible origin of the hilu cell tum the genetic sex of its cells was studied That female ex chr matin was present in the nuclei of these cells is intere tin It seems therefore that the tumor did not develop from em bryonic rests of genetically male cells and presumably the cells secreted male hormone although they were actually e male from a genetic viewpoint The discovery in the ovarin

cortex of polyhedral cells that were morphologically and spatially related to both granulosa and lutein cells could indicate that both tumors originated from cells of the ovarian cortex

Ovarian Interstitial Cell Tumor with Estrogenic Function is described by W P Plate[3] (Utrecht Lanc)

Woman 23 had metrorrhagia associated with a hyperplastic endometrium There were no signs of virilism After operation menstruation became normal At operation the tumor weighed 90 Gm and measured 6.5×6×4.5 cm The cut surface was yellowish white with distinctive yellow spots especially at the periphery Microscopic examination showed complete compression of the cortex caused by the tumor tissue which apparently arose from the medulla A few primordial follicles were visible The tumor consisted of [illegible] cells separated by septa of connective tissue The connective tissue showed localized areas of hyaline degeneration alternating with edematous areas in which scattered isolated tumor cells were found The cells varied in size as did the vacuoles Vacuoles were sometimes absent particularly in the isolated cells Under high power the protoplasm often [illegible] granulation and [illegible] intracellular spaces The nuclei were vesicular spherical [illegible] and had [illegible] lumps of chromatin and one or two [illegible] nuclei The sections were stained with Sudan III and found [illegible] birefringent lipids No glycogen was demonstrable after [illegible] and no red droplets appeared after [illegible] Reinke crystals were not demonstrated with certainty The condition was consequently diagnosed as ovarian interstitial cell tumor

Before operation the urinary excretion of estrogens was increased more than 300 units/24 hours whereas after operation it decreased to less than 200 units/24 hours

A striking feature is that the gonadotrophin excretion which was high before the operation returned to normal after removal of the tumor The following hypothesis might offer a possible explanation Oxidative estrone product can stimulate the hypophysis and induce increased production of luteinizing hormone This patient who showed increased estrogen excretion may have had an excess of the e product

This case demonstrates that interstitial cell tumors can have an estrogenic function An increase in estrogen excretion has been reported in only 1 of the cases of ovarian interstitial cell tumor reported in the literature

Clinical Appearance Diagnosis and Differential Diagnosis of Arrhenoblastoma were studied by H Winzeler J Rattner and A Labhart[4] (Zurich)

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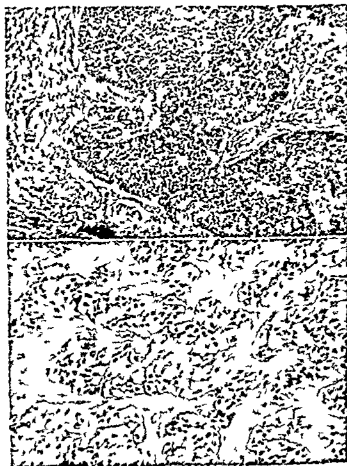


Fig 8 (top) —Typical granul[illegible] with[illegible] ary
Fig 83 (bottom) [illegible]
(Courtesy J Dougherty [illegible] Am J Obst & Gynec [illegible] 653 [illegible] Sept[illegible]ember 1958)

To determine the possible origin of the hilus cell tumor the genetic sex of its cells was studied That female sex chromatin was present in the nuclei of these cells is interesting It seems therefore that the tumor did not develop from embryonic rests of genetically male cells and presumably the cells secreted male hormone although they were actually female from a genetic viewpoint The discovery in the ovary in

cortex of polyhedral cells that were morphologically and topographically related to both granulosa and hilus cells could indicate that both tumors originated from cells of the ovarian cortex.

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Woman, 23, had metrorrhagia associated with a hyperplastic endometrium. There were no signs of virilism. After operation menstruation became normal. At operation the tumor weighed 90 Gm. and measured 6.5×6.5×5 cm. The cut surface was yellowish white with distinctive yellow spots, especially at the periphery. Microscopic examination showed complete *compression of the cortex caused by the tumor tissue*, which apparently arose from the medulla; a few primordial follicles were visible. The tumor consisted of islets of cells separated by septa of connective tissue. The connective tissue showed localized areas of hyaline degeneration alternating with edematous areas in which scattered isolated tumor cells were found. The cells varied in size as did the vacuoles. Vacuoles were sometimes absent, particularly in the isolated cells. Under high power the protoplasm often *showed granulation and collagen tissue was found in the intercellular space*. The nuclei were vesicular, spherical to ellipsoid, and had scanty lumps of chromatin and one or two basophil nuclei. The sections were stained with sudan III and found to contain birefringent lipid. No glycogen was demonstrable after PAS staining, and no red droplets appeared after ponceau fuchsin staining. *Reinke* crystals were not demonstrated with certainty. The condition was consequently diagnosed as ovarian interstitial cell tumor.

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This case demonstrates that *interstitial cell tumors* can have an estrogenic function. An increase in estrogen excretion has been reported in only 1 of the cases of ovarian interstitial cell tumor reported in the literature.

Clinical Appearance, Diagnosis and Differential Diagnosis of Arrhenoblastoma were studied by H. Winzeler, *J.* Kuttner and A. Labhart[4] (Zurich).

(3) [illegible] 26:489-498, Dec. [illegible] 1957.
(4) Schweiz. med. Wchnschr. 87:1556-1566, Dec. 21, 1957.

Woman 22 showed severe amenorrhea and renal hypertension. The latter subsided slowly after removal of a hypoplastic right kidney. During the next 2 years signs of virilism appeared. After extirpation of an arrhenoblastoma a normal menstrual cycle set in and signs of virilism subsided somewhat. *The arrhenoblastoma contained considerable amounts of testosterone, androstenedione, androsterone and progesterone but no estrogens.*

It is felt that the arrhenoblastoma is a hormone producing autonomous organ. The androgenic hormones are probably produced in the large eosinophilic lipid containing cells which cannot be distinguished morphologically from the Leydig cells of the testes or the hilar cells of the ovaries. The clinical picture of pronounced virilism and complete cessation of female functions suggests that the androgen output by the tumor equals that of a healthy male, i.e. 200-300 mg./month.

The patient excreted relatively small amounts of 17-ketosteroids, probably because mainly testosterone was discharged into the circulation, whereas the other steroids, the metabolites of testosterone synthesis, entered the circulation in only limited amounts. The authors suggest that histologically only those virilizing tumors of the ovaries that present a structure similar to that of the testes should be called arrhenoblastomas. They distinguish between hypertrichosis, hirsutism and virilism. Hypertrichosis denotes increased body hair without increase in sexual hair, is independent of hormone production and is found in congenital ectodermal disturbances and in chronic diseases such as anorexia nervosa. Hirsutism is characterized by increased sexual and body hair and by a beard, often accompanied by acne, but not by pathologic changes in the primary or secondary sex organs or in hormonal metabolism. Virilism presents advanced changes in the secondary sex organs which show male traits.

In idiopathic hirsutism the menstrual cycle and fertility are undisturbed and 17-ketosteroids are normal or only slightly increased. The syndrome is due to increased sensitivity of the hair follicle to normal amounts of androgens. There is no endocrine therapy for this condition. In hirsutism with menstrual disturbances a thorough endocrinologic evaluation is important because its severe forms may occur in families with other members afflicted with the androgen

ital syndrome In severe hirsutism with amenorrhea the Stein Leventhal syndrome must be considered Virilism is always a sign of serious adrenocortical or ovarian pathology

Case of Masculinizing Ovarian Tumor Use of Corticosteroid Inhibition Test in Diagnosis is reported by May Cohen Ernest J Maltby and John C Laidlaw (Univ of Toronto)

Woman 38 had virilism and elevated urinary excretion of 17 ketosteroids (14 1 19 8 mg /24 hours) but no abdominal or pelvic mass that could be detected on clinical or radiologic examination Administration of prednisone re ulted in a slight fall in the 17 ketosteroid excretion which averaged 3 7 mg /day This fall was definitely smaller than had been previously ob erved in patients with adrenal hyperplasia but proportionately greater than that noted in patients with adrenal carcinoma This is the kind of response that might be predicted in the presence of an ovarian tumor Hence a provisional diagno is of masculinizing ovarian tumor was made On pelvic laparotomy an arrhenoblastoma of the left ovary was found Postoperatively urinary 17 ketosteroid excretion fell to within normal limits and menstrual periods returned hirsuti m diminished and blood pressure fell from 160/110 to 135/90 mm Hg

Because of the results obtained from the corticosteroid inhibition test in this patient it may be possible to differentiate adrenal from ovarian tumors as a cause of virilism when as is often the case they cannot be localized on phy ical or radiologic examination Such a test would be of little value if the ovarian tumor secreted a large amount of 17 ketosteroids e g over 30 mg /24 hours and if this amount tended to vary greatly from day to day In the pre ence of a masculinizing ovarian tumor with normal total 17 ketosteroid output the corticosteroid inhibition test would be of little diagnostic value

Masculinizing Ovoblastoma of Ovary Report of Case is presented by S W Page[6] (Brisbane Australia)

Girl 16 had amenorrhea for 5 months accompanied by deepening of the voice weight increase and hirsutism The menarchal history was normal Physical examination showed general masculinization large pendulous breasts acne and clitoral enlargement A tumor was palpable in the right fornix There was no evi lence of diabetes mellitus by glucose tolerance test The blood count and blood pressure were normal and there was no osteoporosi A 6 cm well circumscribed tumor replacing the right ovary was removed Microscopically the lesion showed sheets of highly vacuolated cells t lenign

(5) J Cl F [illegible] 1 18 94 97 J ly 1958
(6) J Ot t & ( ) B t Emp 65 11 115 F b y 1958

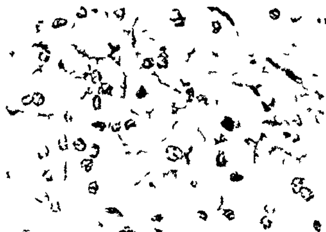


Fig 84 ... (Court... of P... S... W... J Obst & Gynaec Brit Emp ... 1958)

appearance (Fig 84) Doubly refractile material was present in the cells as was sudanophilic lipid After operation the patient rapidly resumed a normal menstrual cycle and subsequently delivered a normal child She did not lactate parturiently Essentially full regression of the virilism eventuated except for permanent deepening of the voice

This patient showed masculinizing changes but no sign of Cushing's syndrome perhaps due to early diagnosis The tumor itself is of disputed histogenesis but is likely related to adrenal rests in the ovary

Testicular Tumors

Leydig Cell Tumor of Testis with Gynecomastia is reported by Jacques Decourt R Tourneur and J Louchart

Man 26 who had had a normal puberty at 15 began to notice unusual sensitivity and enlargement of the breasts Six months later at a prenuptial medical examination male hormone was given with no effect No testicular abnormality was noted Eighteen months after marriage which remained sterile he was referred for study of mammary and testicular anomalies

Body build was essentially normal Height was 1 74 m Some widening of the bitrochanteric diameter was noted Hair development and distribution were normal Gynecomastia was bilateral and symmetrical The mammary glands were the size of a large orange

(1) Ann ... 1 18 80 84 Sept Oct 195

with a reddish areola of 4 cm The gland was moderately firm slightly painful and homogeneous There was no secretion

A testicular tumor the size of a hen s egg distended the scrotum to the right The mass was homogeneous and noninfiltrated and the testis was normally sensitive The head of the epididymis was at the upper pole of the tumor which was solitary The cord was not infiltrated Prostate and seminal vesicles appeared normal to rectal palpation The inguinal and retrocrural glands were spared The rest of the clinical examination was negative

Biochemical changes were moderate Urinary gonadotrophins were 5 10 m u /24 hours 3α steroids were 16 17 keto teroid 8 6

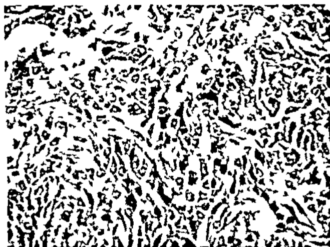


Fig 85—H t l g c t f t (Courtesy of Dec t J f l \ Ler 1 18 80 84 Sept Oct 1957)

mg and pregnanediol 1 3 mg folliculin was 20 μg (normal for adult male 5 10 μg) Spermatozoid count was 4 400/cu mm

The testis was removed and biopsy was performed on the contralateral gland The tumor occupied two thirds of the anterosuperior portion of the gland and did not involve the white tissue It measured 25 mm in diameter was spherical well encapsulated and separated from the seminiferous tubules which it compressed There was no change in the epididymis vagina or cord

Histologically the structure was typically glandular (Fig 85) The cells were grouped in masses or in chains between which were numerous capillaries and were polyhedral or fusiform according to their compression in connective tissue compartments which formed the stroma Cytoplasm was always more or less eosinophilic and slightly granular especially at the periphery without vacuoles or Reinke crystals The nucleus was round and eccentric Some cells were degenerative with a pyknotic nucleus but there was no signifi

cant cellular change Mitoses were rare and the tumor was perfectly encapsulated In places there were recent hemorrhagic suffusions The seminiferous tubules in the tumorous testis had a slightly thickened base and showed complete gonadal maturation with evident reduction in spermatogenesis The interstitial tissue was normal especially extra tumoral Leydig cells Biopsy of the other testis showed nothing abnormal

A few days after operation the patient noted disappearance of mammary tension Examination 3 month later showed little change in gynecomastia Gonadotrophic hormones had a positive limit of 100 units Oligospermia persisted Determination of gonadotrophins a few days later showed normal elimination of 25 50 units

This was a typical case of rare Leydig cell tumor unquestionably benign The moderate degree of biochemical change contrasting with the clinical manifestations suggests that there are increased susceptibility of peripheral receptors abnormal hormonal elimination which is qualitative rather than quantitative and imbalance of secretion of hypophysial stimulants as a result of autonomous secretion by the testis

► [I have previously objected to the application of the term feminization to the gynecomastia resulting from androgenic adrenal tumors on the grounds that mammary development is caused by androgens As the next two papers point out gynecomastia resulted from interstitial cell tumors of the testes without increase in urinary androgen excretion The only mental reservation I hold regarding this apparently established primary production of estrogen by the interstitial cell tumor is that not all androgens can be detected chemically e g following administration of methyl testosterone The actual amount of estrogen in the case of Herrmann Buckner and Paskin was sufficient to permit accurate chemical determination particularly since 48 hour pools were assayed by the expert skill of the late Professor Bauld —Ed]

Interstitial Cell Tumor of Testis with Gynecomastia in a youth 20 is described by W L Herrmann F Buckner and A Baskin[8] (Yale Univ) This is the eighth case reported in the literature Evidence for estrogen secretion was based on clinical grounds and on study of steroid excretion Although urinary estrogen excretion was only slightly above normal the pronounced acute gynecomastia apparent inhibition of the tubular apparatus of the testis with decreased spermatogenesis and decrease in libido and coital power support the concept of estrogenic activity of the tumor

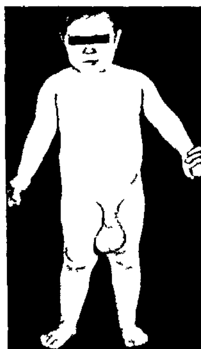
Before removal of the tumor the excretion of androsterone was 1 2 mg/24 hours of etiocholanolone 2 9 mg and of 11-oxy 17 ketosteroids 1 8 mg in contrast to postoperative values of androsterone 1 9 mg/24 hours etiocholanolone

(8) J Clin Endoc [illegible] 18 834 84 Aug t 19 8

5 mg and 11 oxy 17 ketosteroids 1 9 mg Thus the preoperative values of androsterone and etiocholanolone excretion (the urinary metabolites of testosterone) were about one third of the postoperative values whereas the excretion of 11 oxy 17 ketosteroids was unchanged This strongly suggests suppression of normal testicular endocrine function by the estrogens secreted by the tumor

Function of both the tubular and endocrine apparatus of the testis returned to normal after removal of the tumor which was histologically confirmed to be an interstitial cell tumor of the testis

Adrenogenic Testicular Tumor A rare and extraordinary testicular tumor which could only be classified as an undifferentiated carcinoma pathologically with adrenocor



9 F 86—Ad n c t tic l t mo (C t y f C uh R D J U 1 31 M ch 19 8)

tical function is described by Robert D Crouch[9] (Duke Univ) in a boy aged 3 (Fig 86) In view of the pathologic characteristics of the tumor it is impossible to explain the increased steroid excretion The patient showed adrenal insufficiency after removal of the original testicular tumor but responded to treatment with cortisone acetate

Postoperative urinary steroid studies showed 17 ketosteroids of 1 2 mg /24 hour and 17 hydroxycorticoids of 1 2 mg /24 hours as compared to preoperative values for 17 ketosteroids of 18 mg /24 hours and for 17 hydroxycorticoids of 16 7 mg /24 hours Four months later steroid excretion began to rise suggesting metastatic malignancy which was confirmed several months later when a large retroperitoneal mass was removed Prophylactic administration of cortisone before this operation prevented recurrence of adrenal insufficiency Many enlarged nodes that were removed adjacent to the retroperitoneal mass contained no evidence of metastatic tumor

On discharge the patient s steroid excretion was elevated and continued to rise indicating generalized carcinomatosis The patient died several months later but no autopsy was obtained

► [This apparently is the same case which L L Engel and B Baggett described at the Southern Society for Clinical Research Jan 15 1958 They carefully measured the individual compounds produced by this tumor after incubation with labeled acetate testosterone and progesterone The compound produced were androst 4 enedione 3 17 11β hydroxy 4 androst 4 enedione 3 17 adrenosterone 11β hydroxyprogesterone testosterone and dehydroepiandrosterone Adrenal cortical activity is distinctly suggested by 11β hydroxylation In the same report Engel and Baggett described another undifferentiated tumor of the testis which similarly formed 11β hydroxyandrost 4 enedione 3 17 and hydrocortisone on incubation That the testes and adrenal cortex should form identical steroids is not surprising considering their common embryologic origin Perhaps undifferentiated malignant tissue is close to embryologic tissue in nonspecificity of action —Ed]

Seminoma of Testis Following Mumps Orchitis with Atrophy

Report of Case is presented by Arthur W Sullivan and John R Hand[1]

Man 31 noted progressively increasing painless swelling of the left testis He had had mumps with bilateral orchitis when in high school Subsequently both testes had atrophied Because of sterility after marriage he had received a total of 8 800 mg methyltestosterone

(9) J Urol 9 5 7 531 March 1958
(1) B N England Clin 12 1 6 Sept 1958



Fig 87 ( ) ... specimen ... (Courtesy of ...) ... September 1958

over 3 years to produce a rebound phenomenon The left testis was enlarged hard and nodular Chest x ray showed no abnormality Diagnosis was testicular tumor and the testis and surrounding structure were removed (Fig 87) Pathologic diagnosis was seminoma of left testis About 2 months later pain developed in the left lumbar area and a palpable mass was visualized on x ray study The mass thought to be a metastatic lesion from the tumor of the left testis regressed after x ray therapy The patient was free from symptoms 3 years after treatment

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ENDOCRINE INFLUENCES ON NEOPLASTIC DISEASES

► The most hopeful news of the year—Blackburn's announcement of the high order of regressions induced in advanced breast cancer by the administration of 2α methyl dihydro estosterone (Proc Staff Meet Mayo Clin 34 113 Mar 4 1959)—has been detailed in the introduction to this volume References to hypophysectomy and irradiation of the pituitary for advanced breast cancer are included in the section on the Adenohypophysis Hypercalcemia in advanced carcinoma of the breast is described in the section on The Thyroid Gland The remarkable effects of methotrexate on metastatic choriocarcinoma in women are described in the section on The Reproductive System —Ed

Fluoxymesterone Therapy in Advanced Breast Cancer is reported by B J Kennedy (Univ of Minnesota) Objective regression of metastatic breast cancer occurred in 18 (37 5%) of 48 and subjective improvement in 25 (58 %) of 43 patients treated with the halogenated androgen 9α fluoro 11β hydroxy 17α methyltestosterone (fluoxymesterone) The drug was administered orally in doses of 20–40 mg daily to 56 patients 48 of whom had had no previous hormone therapy 8 had had total surgical hypophysectomy

Side effects include masculinizing and erythropoietic changes as noted with other androgenic compound In the doses used degree of hirsutism and acne was less than and the degree of hoarseness oily skin and alopecia the same as with testosterone propionate Increase in libido noted with testosterone propionate did not occur Induced hypercalcemia is a complication as with other androgenic hormone

The antitumor effect of fluoxymesterone is at least as effective as that of testosterone propionate and these preliminary data in a small number of patients indicate that it may be superior to testosterone propionate The ease of administration the less distressing masculinizing effects and the antitumor effect are such that fluoxymesterone may be considered the androgen of choice in treatment of advanced breast cancer

► [As I have noted previously fluoxymesterone is an amazing compound Although it is an extremely potent androgen judged by its effect on the phallus it produces astonishingly few signs of virilization such as beard growth acne deepening of the voice or annoying increase in libido Kennedy reports higher incidence of objective regressions of breast cancer from the administration of this agent than was found by Segaloff and co workers The latter studied a carefully controlled series randomized according to the known variables of predominant site of metastases and age with respect to the menopause Their control group treated with testosterone propionate showed the usual regression rate of about 20% their patients treated with fluoxymesterone had a similar regression rate of 22% (Cancer 11 1187 1958) Thus fluoxymesterone apparently has anti cancer efficacy similar to that of testosterone propionate but produces less distressing virilization Like other 17α alkylated steroids however it seems to be potentially hepatotoxic —Ed.]

Effects of 3 Methylcholanthrene on Endocrine System and Metabolism of Rat and Its Influence to Retard Growth of Mammary Tumors Hitherto Refractory to hormone therapy were noted by Charles Huggins and Lucio Pollice[3] (Univ of

(2) New England J Med 259 6 3 675 Oct. 2 1958
(3) J Exper Med. 107 13 3 J 1 1958

Chicago) Two classes of rat fibroadenoma were used Both were derived from a single mammary tumor of spontaneous origin and were maintained by serial passage in the laboratory for 2 years They differed with respect to hormone dependence class 1 tumors grew rapidly in adult female rats and extremely slowly in ovariectomized or hypophysectomized females or in adult males class 2 tumors grew more rapidly in normal adult female rats and were not much restrained by removal of the ovaries or hypophysis and they grew well in intact male Implants weighing 50 70 mg were made at 8 subcutaneous sites in adolescent Sprague Dawley albino rats Autopsy was performed 40 50 days later

Gastric instillation or intramuscular injection of 3 methylcholanthrene in sesame oil for 50 days resulted in retardation of weight gain reduction in size of transplanted fibroadenomas and decrease in alkaline phosphatase in the inguinal mammary glands The effects were more pronounced with 5 mg than with 2 mg doses Similar results with 1 or 2 mg injections were observed Atrophy of the mammary gland was never observed and hyperplasia of the mammary epithelium was noted in 8 of 50 treated animals

Since growth of class 1 tumors is known to be enhanced by administration of hormones promoting growth of the mammary gland progesterone and 17β estradiol were tested in conjunction with 3 methylcholanthrene Tumor growth when 4 mg progesterone was given with 1 mg 3 methylcholanthrene was less than that in untreated controls and much less than that in rats given the hormone only The gestational growth of mammary tissue resulting from the steroid was not affected by 3 methylcholanthrene nor was there a decrease in alkaline phosphatase Similar effects were seen with 17β estradiol and with combined estrogens

Growth of class 1 tumors was moderately inhibited by 3 methylcholanthrene and markedly impaired by dihydrotestosterone Growth of class 2 tumors was moderately inhibited by either agent alone but profoundly inhibited by a combination of both Rats treated with 2 mg carcinogen and 1 mg dihydrotestosterone had 5% takes compared to 88% in the controls Those tumors which did grow slowly however showed no obvious cytologic differences from the fast growing tumors in untreated animals

The retardation of body growth accompanying 3 methyl cholanthrene treatment could be overcome by force feeding a high protein diet though tumor inhibition was still apparent Use of dihydrotestosterone or ovariectomy more than overcame the weight re training effect

In female rats 3 methylcholanthrene produced a decrease in total body weight in the weights of the uterus and pituitary and in the alkaline phosphatase content of the mammary glands Estrus was rare and atrophy of the vaginal epithelium even more so In male rats total body weight and pituitary weight were reduced compared to control but less markedly than in females The testes were not affected and motile spermatozoa were present in the va at autopsy

The tumor inhibiting properties of 3 methylcholanthrene could be overcome by equine gonadotrophin in dose of 0 05 0 1 unit with 2 mg 3 methylcholanthrene Higher proportions did not increase this effect Tumor growth was retarded but not abolished by 3 methylcholanthrene in hypophysectomized rats and in these animals there was no loss of body weight

Influence of Corticoid Steroids on Frequency of Spleen Metastases in Patients with Breast Cancer was studied by H G Iversen and G H Hjort[4] (*Copenhagen*) The spleen was the organ of choice because frequency of metastases in this organ is rather low

Among 31 hormone treated patients with disseminated breast cancer autopsy showed spleen metastases in 8 among 16 not treated with corticoid steroids no metastases were found in the spleen In patients treated with corticoid steroids histologic examination of the spleen showed atrophy of follicular tissue In 1 instance the spleen tissue was diffusely infiltrated by secondary growths despite the fact that no signs of metastases were noted macroscopically Because of the small number of patients no attempt was made to subdivide them according to dose size or duration of treatment

At autopsy both treated and untreated patients showed numerous metastases in various organs Except for the number of metastases *in the spleen no obvious difference* was

(4) A ta p th et m b l sc l 44 20 1 1958

noted in the number of secondary growths in treated and untreated patients

During treatment with corticoid steroids all organs are affected through the catabolic effects of the hormone but *the most distinct histologic alteration occurs in lymphoid* organs such as the spleen Here the white pulp shows pronounced atrophy To a great extent the lymphoid tissue is responsible for production of antibodies and it is possible that the great concentration of antibodies in the spleen is the chief cause of the low frequency of metastases in this organ Cortisone restrains the formation of antibodies presumably because of compromised nucleic acid metabolism in the antibody producing cells Decrease in the quantity of antibodies is *therefore relatively more* severe in spleen tissue than in other nonlymphatic organs That corticoid steroids increase permeability of spleen tissue and restrain phagocytotic ability of macrophages must also be considered contributory causes to the favored development of secondary growths

It appears that the beneficial subjective effects of cortico steroids *are obtained at the expense of increased cancer spread*

► [This report describes the first clinical counterpart of the tumor spreading action of cortisone noted in animals The catabolic adrenal cortical steroids are capable *of inhibiting defenses against infection and metastasis* so that ordinarily *unsusceptible strains may now be used as hosts* The incidence of objective regressions of advanced breast cancer after administration of adrenal cortical steroids runs somewhere in the neighborhood of [illegible]% The enthusiastic use of these agents by some investigators doubtless stems from observing the euphoria increased appetite weight gain *and polycythemia produced in their patients* Corticoids have a definite place *in the treatment of malignancies* (1) for *hypercalcemia* (2) for hypersplenism and (3) for their subjective effects in terminal care —Ed]

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